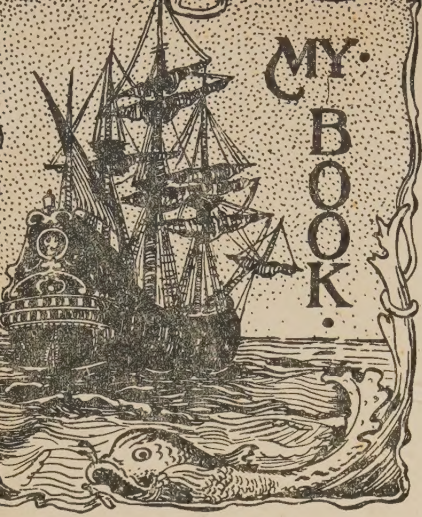

DR. R. LEMLEY GARRARD

R. Lemley Garrard
H. M. S.

THE PATHOLOGY

OF

DIABETES MELLITUS

BY

SHIELDS WARREN, M.D.

PATHOLOGIST TO THE NEW ENGLAND DEACONESS HOSPITAL, THE NEW ENGLAND BAPTIST HOSPITAL, AND THE HUNTINGTON MEMORIAL HOSPITAL, BOSTON; DIRECTOR OF MASSACHUSETTS STATE TUMOR DIAGNOSIS SERVICE; INSTRUCTOR IN PATHOLOGY IN THE HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS

WITH A FOREWORD BY

ELLIOTT P. JOSLIN, M.D.

ILLUSTRATED WITH 83 ENGRAVINGS AND 2 COLORED PLATES

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PHILADELPHIA
1930

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TO

FRANK BURR MALLORY

MY FIRST GUIDE IN THE PATHOLOGY OF DIABETES

FOREWORD.

We fear the unknown and, therefore, I welcome this book which shows what my diabetics must face or rather have faced, but now in large measure can avoid if they will only heed the advice of modern medicine.

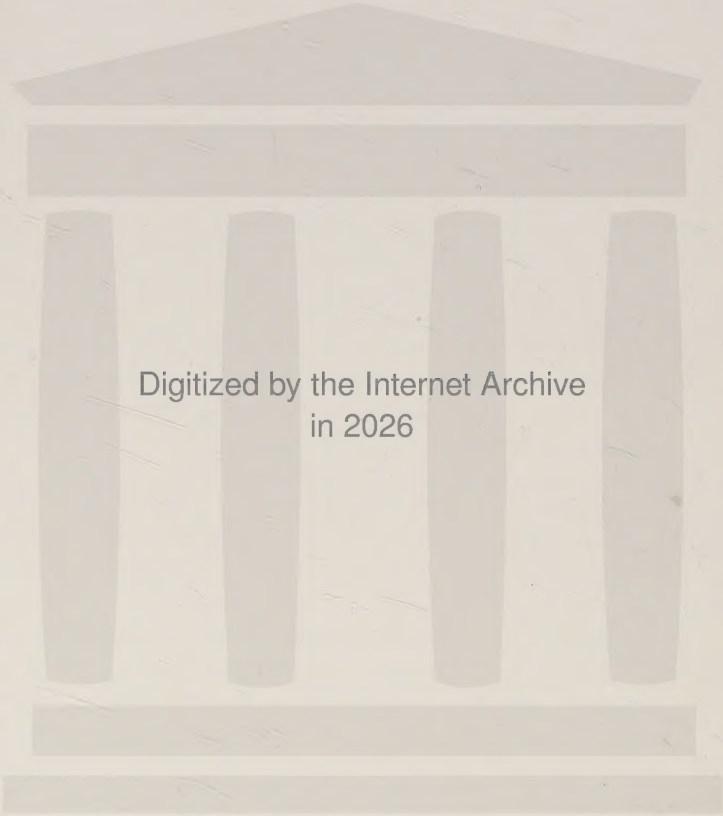
A monograph upon the Pathology of Diabetes does not appear redolent of hope, but as I have watched sentences, paragraphs and ideas and fresh results of hard and thoughtful work go into this volume, I have seen hope creeping in too, and at length have realized that this is a pathology of and for the living almost as much as of the dead. The present diabetic is half and half a surgical and a medical diabetic, and this has afforded Dr. Warren an opportunity to have nearly as many biopsies as autopsies upon which to form his conclusions and he has made the most of it.

The friendliness of other investigators in many laboratories all over the country, which Dr. Warren has experienced, has also impressed me during these months of compilation. This argues well for American medicine, and from it both doctors and patients will profit many fold.

I am thankful that this Pathologist is young; can look with the unbiased, critical mind of youth upon the past; "can grow old along with" diabetes, and especially that the new George F. Baker Clinic for Chronic Disease will adjoin his laboratory. I am grateful for the training he received as Editor of the volume of Preventive Medicine just issued by the Harvard Medical School, because automatically a note of prevention of diabetes and its complications permeates the text.

Some day I wish all who read these pages could visit the modern operating room Dr. Warren has for his patients, for a Pathologist is a Doctor first of all, and there read the motto on the wall—Mortui vivos docent—because then you would come away not dreading to return.

Elliott P. Joslin.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PREFACE.

The longer course of diabetes mellitus with insulin treatment, the growing importance of the complications of the disease, and the failure to elucidate its etiology in spite of the brilliant researches following the discovery of insulin warrant a resurvey of its pathology. To the fundamental morphologic observations of Opie, Ssobolew, Weichselbaum, Sauerbeck, Cecil, Allen and other pioneers in pancreatic pathology but little can be added. It is none the less valuable to compare the pathological anatomy of cases in the Naunyn Era and the Allen Era with that of cases treated with insulin.

Moreover, in diabetes emphasis is happily shifting from the postmortem table to the ward and consulting-room. The pathologist no longer confines his interest in the disease to the pancreatic lesions, but concerns himself also with the tissue changes, often vitally important, secondary to the disease.

In this study use has been made not only of postmortem material from diabetic and non-diabetic patients, but of tissue removed surgically as well. So far as possible, cases of true diabetes mellitus alone have been included, except for certain non-diabetic controls, and cases of renal glycosuria or those in which there has been doubt as to diagnosis have been excluded. The 300 autopsied cases used as the basis of the tables were all definitely diagnosed as diabetes mellitus. A certain number of cases of hemochromatosis and of glycosuria secondary to pituitary lesions have been studied for purposes of comparison.

One of the pleasantest features of this work has been the kindness of many friends in placing diabetic material at my disposal. I am indebted to Dr. E. P. Joslin and his assistants, Drs. H. F. Root and P. White, not only for much clinical material, but also for reading the proof. I wish to thank Dr. F. B. Mallory; Dr. James H. Means and Dr. Tracy B. Mallory; Dr. S. B. Wolbach; Dr. F. Gorham Brigham; Dr. F. H. Lahey; Dr. L. S. McKittrick; Dr. L. W. Smith; Dr. A. M. Greenwood; Dr. C. F. Branch; all of whom have been of great assistance in supplying tissues and clinical data.

Miss Hazel M. Hunt has supervised the chemical and clinical laboratory work on all cases treated in the Deaconess Hospital.

Dr. Howard T. Karsner has very kindly placed at my disposal the large amount of diabetic material in the Cleveland laboratories under his direction, and his assistants showed me many courtesies. Dr. R. H. Jaffé gave me access to the postmortem material of the Cook County Hospital. Dr. R. R. Bensley has generously contributed of his time and counsel, although he is in no way responsible for the opinions expressed here.

To numerous other physicians who have generously aided me with clinical information or material, acknowledgment is made in the text.

I am indebted to the editors of the *American Journal of Pathology*, the *Archives of Internal Medicine*, the *Journal of the American Medical Association*, the *American Journal of the Medical Sciences* and the *New England Journal of Medicine* for permission to make use of material which appeared in their publications.

The technical skill and patience of my assistant, Miss Eva M. Witham, in preparing thousands of sections of diabetic tissues and in compiling the statistical data have been no small factor in making possible the completion of this work. In addition, the preparation of the manuscript and the correction of the proof rested largely on her and on Miss Sadie L. Cooke.

To my publishers I owe many thanks for their constant coöperation.

S. W.

Boston, Massachusetts.

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THE PATHOLOGY OF DIABETES MELLITUS.

CHAPTER I.

DIABETES MELLITUS AND THE PANCREAS.

The name insulin given the pancreatic hormone has by suggestion so thoroughly convinced us of the truth of the insular hypothesis that it is well to examine briefly the evidence upon which it rests at the present time, and to see whether we are justified in accepting it in its entirety. The importance of the truth of this theory with regard to the etiology, treatment and prognosis of diabetes mellitus is obvious. Although Cawley,[1] in 1788, reported a case of diabetes that came to autopsy and showed marked pancreatic damage ("the pancreas was full of calculi which were firmly impacted in its substance . . . the right extremity of the pancreas was hard and appeared to be scirrhous"), the relation of the pancreas to diabetes was not recognized for another century. A few scattered observations[2,3] suggested the importance of this gland in diabetes, but failed to attract any general attention. Only with the discovery of von Mering and Minkowski,[4] that removal of the pancreas would cause diabetes in experimental animals, was the relationship definitely established. Even so, the occurrence of apparently normal glands in many diabetics and the absence of diabetes in individuals much of whose gland had been destroyed by necrosis or by malignant disease were thorns in the flesh of the pathologists for twenty years, and even now there are twinges from the wound. Moreover, Minkowski's experiments showed that the presence of only one-eighth of the pancreas was sufficient to avert the development of diabetes in animals so that the pancreatic lesions found in human cases of diabetes hardly seemed sufficiently severe.

Laguesse[5] hazarded the opinion that the islands of the pancreas were organs of internal secretion, basing this on anatomical grounds, especially the relation of the epithelium of the islands to the rich

vascular network that surrounds it. The first extensive pathological study was that of Hansemann,[6] in 1894, who collected 72 cases from the literature and presented 54 new cases. However, this group was studied chiefly from the standpoint of gross pathology. Hansemann's tables are given below:

TABLE 1.

Cases from the Literature.		*Cases from the Berlin Pathological Institute.*	
Simple atrophy	18	Granular atrophy	36
Chronic interstitial inflammation	18	Fibrous induration with hypertrophy	3
Pancreatic calculi	15	Complicated case	1
Necrosis (? of postmortem change)	6	Normal pancreas	8
Carcinoma	5	Condition not noted	6
Lipomatosis	3		
Fatty degeneration	3		
Abscess	2		
Cyst	1		
Hyperemia	1		
Total	72	Total	54

The granular atrophy of Hansemann is identical with Opie's interacinar fibrosis. It is of more than passing interest that the islands of Langerhans are not mentioned in Hansemann's tables. Indeed, Hansemann was the last as well as the chief champion of the acinar hypothesis, assuming that the acini were the seat of control of carbohydrate metabolism and consistently opposing the insular hypothesis.

At this point we might logically consider the relationship of the islands and acini and the possibility of transitions between the two. However, this can more conveniently be taken up in the chapter on the anatomy and histology of the pancreas.

The transplantation of the remaining portions of partially resected pancreases by Hédon[7] with the failure of diabetes to develop as long as the transplants remained in healthy condition served to show that an internal secretion and not the external were concerned in carbohydrate metabolism. The observation of Opie[8,9] and Ssobolew[10] localized in the islands the pathological changes associated with diabetes and explained, at least in part, the previous difficulties in correlation of the clinical and pathological findings. In cases of diabetes mellitus the islands were frequently diseased with or without damage of the acinar tissue, while in cases of extensive pancreatic lesions with normal carbohydrate metabolism,

such as some cases of acute pancreatic necrosis or carcinoma, the islands were found to be intact. The abnormalities in the islands were either qualitative, as sclerosis or hyalinization, or else quantitative. Ssobolew described complete absence of islands in 4 out of 15 cases of diabetes. This finding is most remarkable. Probably if he had had the advantage of the specific staining methods for the island cells discovered by Lane,[11] Bensley[12] and others he would have found at least some island tissue present.

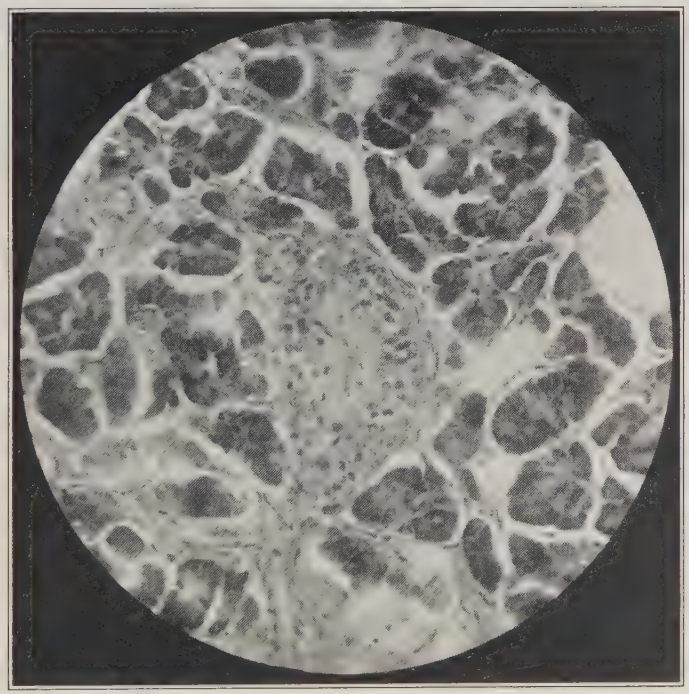

FIG. 1.—Moderate hyalinization of island of Langerhans. Male, aged sixty-six years. Duration of diabetes fourteen years.

In 1904 Sauerbeck,[13] analyzing the available evidence, championed the insular hypothesis and it has remained the favorite up to the present. Opie[14] presents a table (page 20), based on cases compiled by Sauerbeck (176) and himself (112).

Heiberg[15] and Weichselbaum[16,17] each claimed pancreatic changes to be present in every case of diabetes and to be limited to the islands in a sufficient number of cases to prove the insular hypothesis.

Cecil,[18] in a series of 90 cases, came to the same conclusion and later[19] called attention to the frequent occurrence of evidence of regeneration or hypertrophy in the islands of Langerhans in diabetes (34 out of 100 cases). Similar changes suggesting hypertrophy and regeneration were found in cases of chronic pancreatitis without diabetes. The presence of regenerative processes in the islands was also stressed by Weichselbaum[20]—both cellular proliferation of the island epithelium and the formation of new islands from the epithelium of the ducts. With all this evidence favoring the insular hypothesis there was nevertheless an under-current of discouragement, of dissatisfaction with the available means of recognizing characteristic lesions in diabetes. This feeling was well expressed by Allen[21] seventeen years ago, and his statement even today holds true: "Every anatomical hypothesis of diabetes still requires to be assisted by assuming the existence of a certain proportion of functional cases without known anatomical basis."

Table 2.—Pancreatic Lesions Shown by Cases Compiled by Sauerbeck and Opie.

Interacinar pancreatitis	125
Interlobular pancreatitis	13
Lipomatosis	18
Calculi	9
Cyst	1
Carcinoma	5
Focal necrosis	2
Atrophy	65
Lesions of islands with normal parenchyma:	
Hyaline degeneration	6
Sclerosis	2
Adenoma-like hypertrophy	3
No lesion of pancreas:	
Pancreas normal	34
Number of islands diminished	5
Total	288

With the differentiation by Lane[11] of α and β cells in the islands of Langerhans, and with the beautiful studies of Bensley[12] on the pancreas of the guinea pig, it was natural to attempt to correlate cytological with clinical findings in the hope that there might be found some single, universal diabetic lesion. Homans[22] found disappearance of the secretory granules in the island cells of cats from which three-fourths of the pancreas had been removed. In those animals which became diabetic he noted hydropic degeneration of the island cells, and hence regarded them as the site of the carbohydrate-regulating function. This hydropic degeneration, previously noted by Weichselbaum[20] in diabetic patients and which

Allen[21,23] had produced experimentally in dogs, Homans[24] found to affect chiefly the β cells.

This gave new hope for the existence of a single characteristic, universal diabetic lesion. Further study has unfortunately blasted this hope. Hydropic degeneration of the β cells may well mean diabetes when it occurs, but by no means all diabetic pancreases show this lesion.

In the meantime the duct ligation experiments of Schulze,[25] Ukai[26] and others[27,28] showed that extensive (though now known to be incomplete) atrophy of the acinar tissue was unaccompanied by disturbance of carbohydrate metabolism.

Insulin[29] was the climax of this line of experimentation. In spite of the important evidence adduced by the production of insulin from the principal islets of fish[30,31] and from pancreatic tissue in which the acini had practically disappeared secondary to duct ligation, the production of insulin in the entire absence of acini was not yet proved.

It remained for Wilder's[32] striking case of hyperinsulinism due to carcinoma of the islands of Langerhans to clinch the truth of the insular hypothesis. This was further reinforced by the carcinoma of Thalhimer and Murphy,[33] the adenoma of McClenahan and Norris,[34] and by the results of the operative removal of the carcinoma of island-cell type reported by Howland.[35] Less conclusive are the results of operative removal of portions of the pancreas in cases of hyperinsulinism as reported by Allan[36] and Finney.[37] Alleviation of symptoms on removal of a portion of the whole pancreas, of course, gives no evidence as to whether the islands, the acini, or both are primarily involved.

THE ACINO-INSULAR HYPOTHESIS.

That the malfunction of the pancreas as a whole is responsible for diabetes is the essence of the acino-insular hypothesis. Lombroso[38] has presented good evidence for this theory. In the hands of some other proponents, such as Reitmann,[39] who believed that normally islands and acini both controlled carbohydrate metabolism, yet either alone could perform this function; and Karakascheff,[40] who believed the islands were only of use to replace worn-out acini and were not separate organs, this theory was decidedly weak. While Laguesse[41] has valiantly upheld the possibility of reciprocal transitions between acini and islands, he nevertheless believes the islands to be primarily concerned with carbohydrate metabolism.

Herxheimer[42] believed that when the acinar tissue is injured the islands can supply internal secretion.

This hypothesis is a logical corollary of the transition theory of interrelation of islands and acini which will be discussed in Chapter II. Saguchi[43] has recently suggested, on the basis of changes in the Golgi apparatus and lipoid corpuscles of the acinar cells, that they may take part in the production of the internal secretion of the pancreas.

A monograph of Seyfarth[44] sums up the evidence and perhaps marks the high-water mark of the prestige of this theory, although the possibility of its truth cannot but lurk in our minds.

THE ACINAR HYPOTHESIS.

Of historical interest alone is the belief of Hansemann[6] that the acinar cells are the seat of regulations of carbohydrate metabolism. He laid great stress on "granular atrophy," essentially interacinar fibrosis, as the most important lesion in diabetes.

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CHAPTER II.

THE NORMAL PANCREAS.

The relation of the pancreas—particularly its islets—to carbohydrate metabolism is so marked as to necessitate a thorough understanding of the normal histology of the gland in any consideration of the anatomical pathology of diabetes mellitus.

Few organs of the body are less constant in size and architecture than the pancreas. The descriptions given in most textbooks of anatomy cover the essential features of the gland but give altogether too great an impression of its constancy in morphology. For example, the weight at autopsy in individuals showing no evidence of pancreatic disorder ranges from 60 to 160 grams, averaging about 95 grams. One of the best descriptions of the pancreas is that of Opie,[1] and this has been freely drawn upon in the present discussion.

In the loop of the duodenum lies the head of the pancreas. From the upper and anterior aspect of the head a constricted portion, the neck, bends slightly upward and forward and then stretches to the right, forming the body of the gland. Behind the neck pass the superior mesenteric vessels. The body tapers slightly toward the spleen and this thinner portion of the gland is called the tail.

The development of the pancreas takes place from three primitive outgrowths from the mid-gut, one of which is on the dorsal surface between the liver and the stomach, and the other two a right and a left ventral, which subsequently fuse and rise on either side of the hepatic duct and then grow to meet the dorsal part. With the alteration in position of the stomach and duodenum the pancreas is changed in position so that the dorsal portion lies transversely, with its left extremity near the spleen, and the ventral portion is carried with the torsion of the duodenum to the right and backward. Thus, with further growth the part of the pancreas which was originally ventral comes in contact with the larger dorsal part and unites with it, as a rule, during the second half of the second month of embryonic life.

In studies on 21 human embryos, Pearce[2] found the islands to appear first in the 54 mm. embryo as oval eosinophilic cell masses

continuous with the acini. During the third month of development, a few completely separated islands were found, while most remained connected with the acini by solid stalks of cells. Each island was provided with four to seven afferent and efferent capillaries. Development is not infrequently arrested in congenital syphilitic pancreatitis, and islands are found still communicating with acini. In light of the studies of Bensley and others, the islands probably have a common origin with the acini from the duct cells, rather than arising from the acinar cells.

The pancreas is traversed from left to right by the duct of Wirsung, which bends downward and backward in the neck, and after traversing the posterior surface of the head, reaches the wall of the duodenum, where it unites with the common bile duct. The accessory pancreatic duct, that of Santorini, arises in the upper portion of the head and terminates in a small papilla in the mucous membrane of the second portion of the duodenum about 2 cm. above the papilla of Vater.

There are numerous variations in the distribution of the ducts and their anastomoses. In 100 pancreases Opie[1] found the ducts in anastomosis in 90. He gives a number of excellent diagrams of the relationships of the two ducts.

On the surface of the pancreas irregular areas are demarcated by loose connective tissue and fat. The amount of this fat varies greatly with the state of nutrition of the individual, and is one of the chief factors in the variability of weight of the gland. The gland can be divided by dissection of the tissue into clear-cut lobules, usually about 1 cm. in diameter. These primary lobules are subdivided into smaller secondary lobules, usually several millimeters in diameter, by poorly-defined septa. With the low power of the microscope these secondary lobules may be still further divided to tertiary lobules.

The blood supply of the body and the tail of the pancreas is from branches of the splenic artery, whereas the head receives its supply from the superior pancreatico-duodenal artery, a branch of the hepatic, and from the inferior pancreatico-duodenal artery, a branch of the superior mesenteric. The bulk of the venous blood from the pancreas passes into the splenic vein and a smaller amount into branches of the superior mesenteric vein.

The gland is innervated by fibers from the lienal plexus, which in turn is formed by branches from the left celiac ganglion, the celiac plexus and the right vagus nerve. Pacinian corpuscles are not rare.

THE HISTOLOGY OF THE PANCREAS.

The following description of the pancreatic cells is based on the study of human autopsy material fixed from twenty minutes to three hours postmortem. No pancreas showing gross evidence of pathological change was included. In addition, the information disclosed by the far more careful researches of Bensley,[3] Laguesse,[4] Ukai[5] and many others has been liberally drawn upon.

Supposedly normal pancreatic tissue was fixed routinely in Zenker's fluid, sublimate-bichromate and formalin. Frequently Champy's fluid, Zenker-formol, acetic-osmic-bichromate, osmic acid, absolute alcohol and Regaud's method were also resorted to.

The following stains were used on all pancreases:

Phloxine-methylene blue.
Phosphotungstic acid hematoxylin.
Mallory's aniline blue.
Goodpasture's eosin-methylene blue.
Masson's iron hematoxylin-vert lumière.
Iron hematoxylin-Van Gieson.
Ukai's stain.
Bensley's neutral gentian.

On certain favorable cases various lipoid stains were employed, as were Best's and Langhan's methods for glycogen. When the tissue was fresh and properly fixed the aniline fuchsin-methyl green or picric acid method or the iron-hematoxylin method for mitochondria were employed, as were Bensley's safranin stain and a very useful modification of Mallory's aniline blue stain devised by Bensley.[6] This last is given below:

1. Altmann's aniline fuchsin, ten minutes.
2. Wash rapidly in distilled water.
3. Phosphomolybdic acid, 1 per cent solution, ten minutes.
4. Stain in aniline blue, orange G.
5. Dehydrate.
6. Clear and mount in xylol balsam.

Duct Cells.—The simplest system in the pancreas is that of the ducts, with which may be included the centro-acinar cells. Moreover, from the primitive duct epithelium the external and the internal secretory elements of the gland are derived. As would be expected from their origin from the duodenal epithelium, the ducts at their proximal ends are lined by epithelium closely resembling that of the duodenum—tall, columnar cells with distally placed

elongate nuclei. Granules varying in size which give the characteristic staining reactions of mucin occasionally occur in the proximal portion. True goblet cells occur with varying frequency. Near the duodenum, the epithelium and the basement membrane are thrown into papillary folds, but as the ducts become finer these disappear. The similarity of this epithelium to that of the extrahepatic biliary passages is very striking. At times even the neoplasms derived from the two are practically indistinguishable histologically. The ducts are supported by relatively thick bands of connective tissue made up chiefly of collagen fibers but containing a few elastic fibers. Imbedded in this connective-tissue stroma, particularly near the duodenum, small mucous glands similar to Brunner's glands are scattered.

The mucous secretion of the cells disappears and the epithelium gradually changes from columnar to cuboidal as the ducts become finer. There is a tendency for the duct epithelium to flatten slightly in the intercalated ducts, and frequently the centro-acinar cells flatten very abruptly. The centro-acinar cells are similar in appearance to the cells of the finer ducts and probably represent the termini of the ducts. They tend to insinuate themselves about the apices of the acinar cells.

Both duct cells and centro-acinar cells have a clear, acidophilic cytoplasm, free from secretory granules and chromidial substance. In favorable cases I have found scattered, fine, rod-shaped mitochondria in both duct cells and centro-acinar cells. Nassanov[7] demonstrated a simple Golgi apparatus in these cells. It is much less complicated than in the acinar and island cells.

The nucleus is usually oval, smaller than that of the acinar cell, and relatively rich in chromatin. The nucleolus, so prominent in the acinar cell, is not obvious. Extremely rarely mitosis is seen, even in adults.

Bensley[3] has demonstrated in the guinea pig, through vital staining with pyronin, a system of fine anastomosing tubules surrounding the larger ducts and communicating with the ducts on the one hand and the islands of Langerhans on the other. Moreover, scattered in these tubules are single cells identical with those of the islands. Otani[8] found in human cases d rect connection between a moderate proportion of the islands and the interlobular or intralobular ducts.

Acinar Cells. That portion of the pancreas with which we are best acquainted is the external secretory system. The obvious importance of the pancreatic ferments and the striking appearance

of the acinar cells early focussed attention on the cytology of the latter. The easy demonstration of the zymogen granules made attempts at correlation between changes in the intracellular structure and glandular secretion peculiarly enticing.

With any of the ordinary stains the cytoplasm of the acinar cell is clearly divided into two zones. The inner zone is markedly vacuolated, and with appropriate staining these vacuoles are seen to contain, or rather be, the zymogen granules. The outer portion of the cell, usually containing the nucleus, stains strongly with basic dyes and is faintly striated. Thus, when stained with Goodpasture's methylene blue after chrome-sublimate or Zenker-formol fixation, the outer portion of the cell shows a diffuse bluish clouding (chromidial substance) with faint, clear striations. These striations are known to be due in animals to the presence of mitochondria. While I have had great difficulty demonstrating mitochondria in human pancreatic tissue, in several cases I have found them to have this same distribution. Acetic or osmic acid in the fixing fluid causes the chromidial substance to be precipitated in filamentous form (Bensley).[3] However, Saguchi[9] believes these filaments are in reality preformed, and simply made visible by the acid.

In the human cases in which I have found mitochondria they appear as fairly long, slightly wavy rods of moderately irregular thickness, arranged more or less parallel to the long axis of the cell and only very rarely occurring in the inner or vacuolated zone. I have not been able to detect any definite relation between mitochondria and zymogen granules.

With stains such as phosphotungstic acid hematoxylin following formalin fixation, or as Bensley's neutral gentian, the zymogen granules are the most prominent elements of the cell. These granules vary in size, but are fairly coarse. Their origin is still in dispute, being considered as mitochondrial derivatives, products of the Golgi apparatus or of the chromidial substance. Even the nucleus has been thought their source.

Occasionally there are scattered foci of cells, ranging from a portion of an acinus to several adjacent acini in size, which stand out markedly acidophilic with eosin-methylene blue staining. These cells have a clear homogeneous cytoplasm and apparently do not contain either zymogen granules or chromidial substance. These are more likely foci of exhausted cells rather than foci of necrosis. They throw some light on the supposed transition of acinar to island tissue, as in casual examination of a section they strongly

resemble islands. However, these cells never contain the specific granules of the island cells, and their arrangement is in no way characteristic of islands.

Island Cells. Distributed irregularly in the pancreatic parenchyma are the groups of small polygonal cells with homogeneous cytoplasm first described by Langerhans.[10] These cell groups vary greatly in size, but most are between 75 and 175 micra in diameter. The variation in number is also great. Bensley[3] has counted as many

FIG. 2.—Normal pancreas showing acini, islands and a duct. Male, aged forty-six years. Non-diabetic. Phosphotungstic acid hematoxylin stain. × 170.

as 56,000 in the pancreas of the guinea pig, and found an average of 22.3 per c.mm. in adult guinea pigs. Clark[11] found from 250,000 to 1,750,000 in the pancreases of non-diabetic adult humans. Owing to variation in distribution, even in the same pancreas, estimates of the number of islands present are of but little value. They are, however, two to four times as frequent in the tail as in the remainder of the organ. Heiberg[12] estimated that the islands made up approximately 3 per cent of the pancreatic tissue.

Until the work of Bensley[3] the distinguishing characteristics of the island cells were chiefly negative, the most important being the absence of zymogen granules. Specific granules had been demonstrated in the island cells by Laguesse,[13] in 1896, and the presence of two different types of cells having been detected by Schulze[14] and Diamare,[15] the path for further study was opened by Lane,[16] who devised methods for distinguishing the two types of granules from one another and also from the zymogen granules.

Two types of island cells are commonly recognized, the α cells and the β. Unstained, the granules of the two different types of cells cannot be distinguished from one another. The granules of the α cells are stained violet by safranin-acid violet following Lane's chrome-sublimate fixation, and the β granules are stained red. With the same fixation and acid fuchsin after the neutral gentian stain the α cells are red and the β cells violet. With the modification of Mallory's aniline blue, which I have found very useful, the α granules are stained red and the β granules are stained bluish-purple. (See Plate I.) This same result is obtained by Ukai's stain.

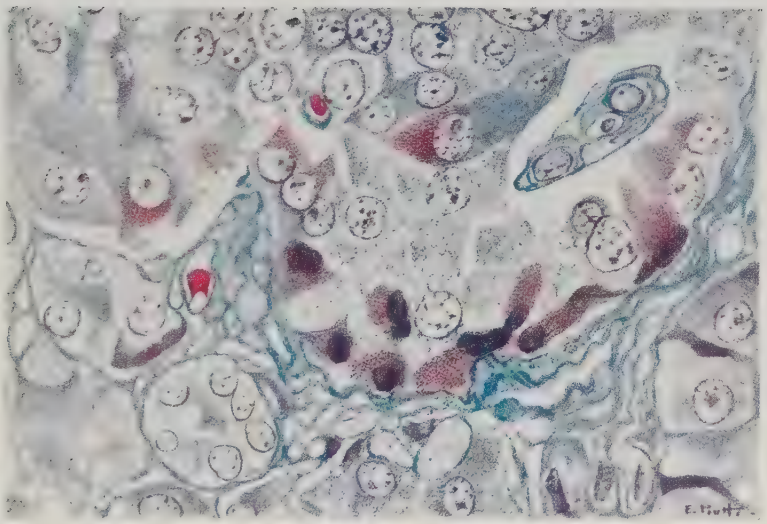
Bensley[3] noted that, in preparations where the granules of the island cells were not preserved or were not stained, the protoplasm is finely alveolar, and that as postmortem degeneration progresses, a coarser alveolar structure appears. This has an important bearing on the question of hydropic degeneration.

In addition to the presence of specific granules the types of island cells can be distinguished by nuclear characteristics. Both types of island cells lack the prominent nucleus of the acinar cell. The nuclei of the α cells are poor in chromatin and are usually oval in outline. The nuclei of the β cells are usually spherical, though sometimes slightly oval, and contain relatively large granules of chromatin. In addition to these two types of cells, cells are found without granules whose nuclei closely resemble those of the α cells. The β cells form the greater bulk of the island.

In the guinea pig Bensley[3] found no definite arrangement of the α and β cells in the islands. They also occur without definite arrangement in islands of the human pancreas, although the α cells appear a little more frequently at the periphery of the islands.

Tschassownikow[17] suggested that the α cells were intermediate between the acinar cells and the β cells. However, Bensley[3] has shown that they occur in large numbers in the interstitial islands which are developed directly from the ducts, they are present in the interior of the island as well as at its periphery, they are present

PLATE I



Normal Pancreas.

α cells contain orange-red granules, β cells bluish granules. The duct epithelium stains a very light blue. The acinar cells stain bluish-purple. By a slight modification the zymogen granules can be shown in bright orange but are not stained here. Note in the upper left-hand corner the marked vacuolization of several of the island cells suggesting hydropic degeneration. Note also the vacuolization of the island cells in the central lower portion of the island which is shown by suitable methods to be due to the presence of fat. In comparison with Fig. 18 this shows that the amount of fat demonstrated there is not excessive. No. 3197. Female, aged fifty-seven years. Non-diabetic.

in the acini of new-born guinea pigs without β cells, and they disappear within the first week of life without any increase in the number of β cells. Bensley concludes that the two types are independent and that each develops from an undifferentiated duct cell.

In addition to the granules the island cells contain mitochondria which appear as delicate filaments and fine granules. They are scattered throughout the cell in marked contrast to their concentration at the base of the acinar cell.*

Saguchi[9] has described in the frog's pancreas five types of island cells which have transitional forms between certain of them. In human tissue I have been unable to parallel Saguchi's types.

Mitotic figures are occasionally encountered in the island cells of normal pancreases. An example is shown in Fig. 19, from the pancreas of a male, aged forty-five years, dying from pneumonia.

Transition Theory.—The possibility of transition between island and acinar cell is obviously of great importance, particularly in the diabetic pancreas. However, there is now little but historical interest in the question, thanks particularly to the masterly studies of Bensley. The evidence brought forward by Laguesse,[18] Dale,[19] Vincent and Thompson[20] to support the transition theory faded before the demonstration of specific granules in the island cells. Saguchi[9] holds that the granules of the α and β cells do not take active part in the specific secretion of the island cells but that the E cells, with their lipoid corpuscles and urano-argentophile apparatus, are the most important. He further believes[21] the acinar cell may possess an internal secretion. Saguchi believes that the acinar cell may change into an island cell, with changes not only of the cell body and nucleus but of the intracytoplasmic structures as well.

Otani[22] has also endeavored to revive the old controversy, basing his evidence for transition between the islands and the acini not so much upon the specific character of the island cells as on the arrangement of the cells and the relations of the islands to the acini, laying special stress on the absence or presence of the capsule.

The existence or non-existence of a connective-tissue capsule about the island has been regarded as of importance by many in determining the entity of the island-cell group. The "Kapsul-

* O'Leary, J. L. (Anat. Record, 1930, **45**, 27) has followed *in vivo* the formation of vacuoles within the island cells and the migration of these vacuoles toward the capillary end of the cell, where they gradually decrease in size. It is possible that these may be secretory vacuoles. It may be that the appearance of hydropic degeneration is due to the formation of large numbers of these vacuoles.

Frage" has been hotly contested. However, the frequent occurrence of an imperfect connective-tissue capsule is undeniable – also its usually incomplete character. A complete connective-tissue capsule is usually the first sign of a developing fibrosis.

Otani[8] recognizes three types of island structure:

1. Most common: Islands connected with surrounding acini.
2. Islands connected with ducts.
3. Least frequent: Islands strictly separated from the surrounding structures.

In the same pancreas he finds wide variations in size, shape and relation of the islands. In addition he believes[22] that acinar cells are able to change into island cells and that the process of hypertrophy of the islands of Langerhans in the adult pancreas is mostly due to transformation or hyperplasia of acinar and centro-acinar cells. He does not consider the islands as constituting an independent tissue. He also concludes that new formation of the islands of the adult pancreas may occur by transformation and hyperplasia of acinar, centro-acinar or duct cells. The striking experiments of Ukai[5] have emphasized the independence of the island tissue from the acini and have also shown that the insular epithelium is apparently possessed of greater resistance to injury, if not greater powers of regeneration, than is the case with the acinar cells.

Blood Supply.—One of the most striking of the grosser proofs of the autonomy of the islands, and one of the most important facts from the standpoint of their function, is their peculiar blood supply.[23] Whereas the acinar tissue receives a liberal blood supply from the lobular arteriole with its interacinar capillaries, the islands receive an extraordinarily rich supply, and have wide anastomosing sinusoids in almost glomerular arrangement coursing through them. This sinusoidal net is usually fed from one or more arterioles, but sometimes is in direct continuity with the interacinar capillaries. In a recent case of marked chronic passive congestion placed at my disposal by Dr. S. B. Wolbach, this rich supply is even better shown than by injection preparations.

Nerve Supply.—Between the island cells are the termination of numerous nerve fibers, which form a network around the islands.[24] Pensa[25] detected numerous nerve fibers entering the islands with the blood vessels and distributed along them and between cells. These fibers he felt to be different in number and arrangement from those supplying the acini. Rarely small ganglia are encountered.

Pacinian corpuscles are present in the human pancreas, and are very common in that of the cat.

An excellent general review of the cytology of the pancreas has been written by Opie.[26]

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CHAPTER III.

THE PANCREAS IN DIABETES MELLITUS.

Few diseases definitely associated with any one function, metabolic or otherwise, show as wide a range of concomitant pathological change as does diabetes—or as frequent absence of demonstrable pathological change.

First the demonstrable pathology in the islands of Langerhans may be considered. These changes may be qualitative or quantitative. To a pathologist qualitative changes are always more intriguing, and these will be considered first.

QUALITATIVE VARIATIONS IN THE ISLANDS OF LANGERHANS.

Hyaline Change.—Hyalinization of the islands of Langerhans, although described nearly thirty years ago[1] and now generally considered the most typical pancreatic lesion in diabetes mellitus, is still somewhat of a puzzle. The nature of the process and the mechanism of its selective localization in the islands are as yet in controversy. In the excellent review by Opie,[2] one viewpoint is stated as favoring an epithelial, and hence intracellular, origin for this hyaline substance, while the other leans toward a mesoblastic intercellular origin. Weichselbaum[3] believed the hyaline change to be secondary to fibrosis, and a result of fibroblastic activity. Mallory[4] has in a few instances succeeded in obtaining from it typical staining reactions for amyloid.

Obviously it is important to know whether the island cells are merely being replaced by hyaline derived from their own substance after succumbing to some injury, or whether they are being strangled by gradually increasing deposits of hyaline laid down in and about the stroma of the islands. Or in cruder form, is hyalinization of the islands the result or the cause of diabetes in those cases in which it is present?

If this hyaline were epithelial in origin and a product of degeneration of island cells we should find it as commonly in young diabetics

as in old, and we never should expect to find it in the absence of diabetes. However, of 89 cases of hyalinization of the islands in diabetes that I have studied, 96.6 per cent occurred in individuals over forty years of age. At this age hyaline changes begin to be noted in the smaller blood vessels, particularly those of the spleen, an organ, which, incidentally, lies in almost the same vascular circuit as does the pancreas.

In spite of this preponderance of hyalinization of the islands in the older age groups, curiously enough, the first case to be described (Opie[1]) showing this lesion was that of a girl, aged seventeen years, whose diabetes began two years before death.

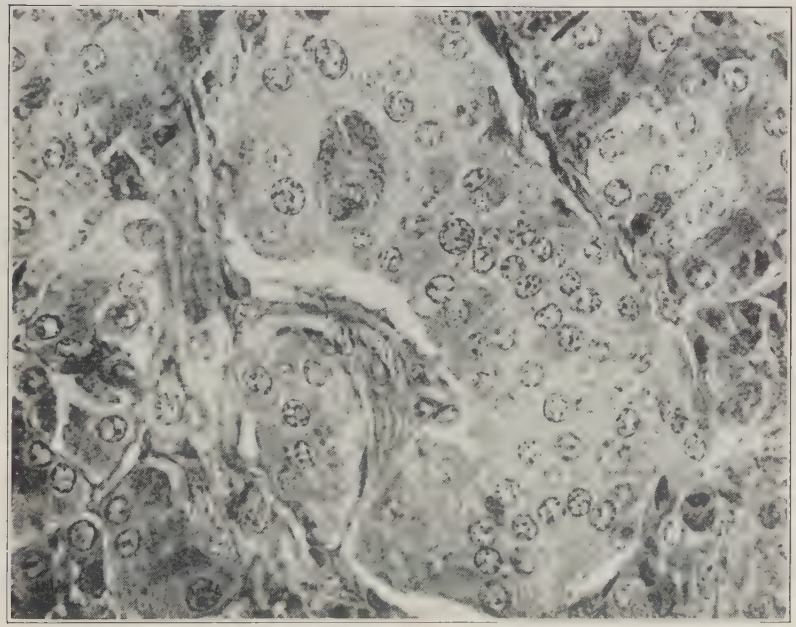

FIG. 3.—Island showing large degenerating cell. No. 3515. Female, aged forty-eight years. Duration of diabetes three years. Mallory's aniline blue stain. × 560.

One of the arguments brought forward in favor of the epithelial origin for hyaline in the islands is that with Mallory's aniline blue stain certain of the island cells, assumed to be those which later will be replaced by hyaline, stain intensely blue and that later masses of hyaline appear in them which ultimately fuse, forming large masses about the capillaries. One of these cells is shown in Fig. 3.

In many cases of diabetes examined in this laboratory, bluish staining cells similar to those described can be seen, provided the tissue is fresh and the fixation satisfactory. As a rule, they are somewhat irregularly distributed through the substance of the islands. At other points small masses of hyaline can be seen. However, similar blue-stained cells can be found in the islands of non-diabetic individuals and in islands which showed no trace of hyalinization. The blue-stained cells occur scattered throughout the island and do not show the definite relationship to the blood vessels that the hyaline does.

Although admittedly unreliable, the staining reactions of this hyaline throw some further light on its nature. In the first place, out of 51 cases of hyalinization of the islands suitably fixed, following the suggestion of Dr. F. B. Mallory, I have been able to demonstrate a positive amyloid reaction with methyl violet or iodine green in 14. Although the hyaline does at times give the reactions for amyloid, nevertheless diabetes associated with amyloid disease is rare, and in generalized amyloidosis the islands, as a rule, show no involvement. However, the capriciousness of amyloid deposition is well known, and local "amyloid tumors"[5,6] may be encountered, particularly in the nasopharynx, although there is none elsewhere in the body.

The hyaline ordinarily gives the following staining reactions:

Mallory's aniline blue—translucent blue.
Phosphotungstic acid hematoxylin—brown.
Phosphomolybdic acid hematoxylin—deep blue.
Eosin-methylene blue—pink.
Masson's iron hematoxylin blue—translucent blue.
Masson's iron hematoxylin green—bright green.
Iron hematoxylin-Van Gieson—yellowish.
Best's carmine stain—pink to old rose.

The staining reactions obtained from hyaline about the arterioles of the spleen from several cases which also showed hyalinization of the islands of Langerhans, were identical. Occasionally a slight fibrillar structure can be demonstrated in the hyaline.

Study by the serial section method shows that the masses of hyaline are always in contact with the walls of the vessels of the islands, and always intercellular. Masses that are apparently isolated can always be traced in the course of one or more sections 3 microns thick to the perivascular deposit of which they are a portion.

Should hyaline be the result of cellular degeneration secondary to diabetes, it ought never to be present in the absence of diabetes. However, cases have been reported by Cecil,[7] Wright[8] and others where hyalinization of the islands was present in non-diabetics.* It is true that in a few of these cases objections can be raised on the ground that the individual might be in reality diabetic, but owing to terminal malnutrition failed to show signs of diabetes, just as they might fail to show these signs under rigid dietary treatment. But not all these cases can be thus disposed of.

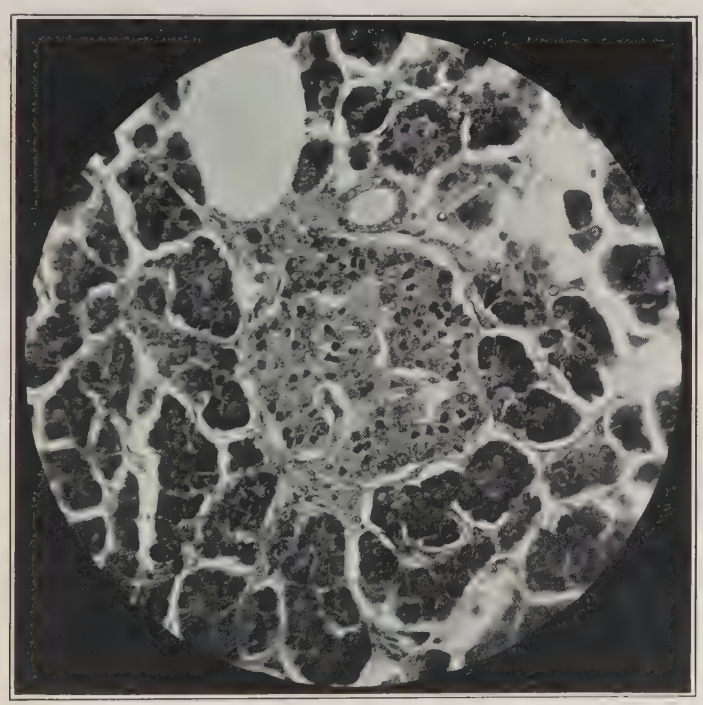

FIG. 4.—Very early hyalinization of island of Langerhans. M979. Male, aged sixty-six years. Duration of diabetes fourteen years. × 170.

Moreover, of 4 cases of my own where fairly complete clinical data has been available to rule out the occurrence of diabetes mellitus, hyaline has been present in the islands to a moderate degree in 3 cases and to a marked degree in 1.

Hyaline degeneration is most common in older diabetics, as has

* See also page 72.

already been said, and in mild diabetics. In carefully studied cases definitely known to have had diabetes over ten years, 50 per cent showed hyalinization of the islands of Langerhans.

A striking feature is the unequal involvement of the islands in the same pancreas, some being converted to completely hyalinized masses, with only a few fibroblasts and capillary endothelial cells present, while others may be completely spared. Still others show varying degrees of transition between these two extremes. This

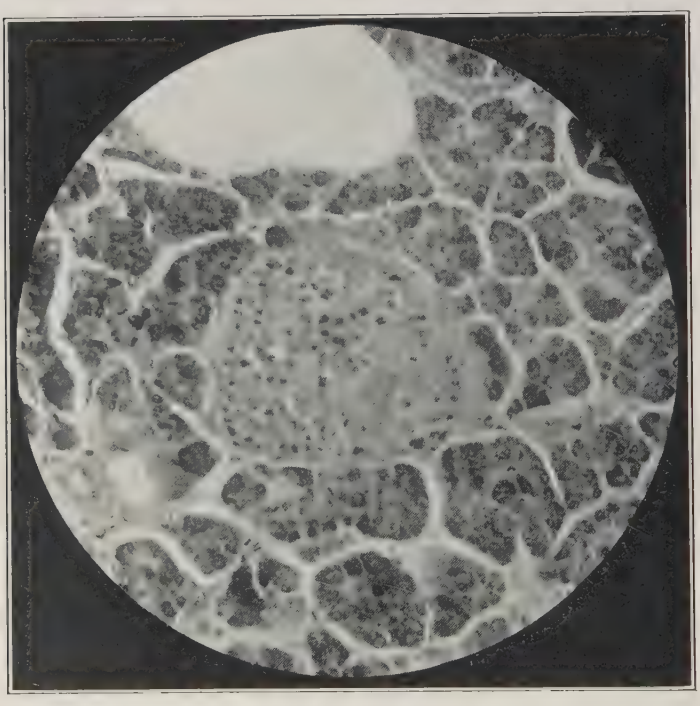

FIG. 5.—Early hyalinization of island of Langerhans. M979. Male, aged sixty-six years. Duration of diabetes fourteen years. Eosin-methylene blue stain. × 170.

seems to point to either striking inequalities of involvement or to the replacement of destroyed islands by new.

Frequently the insular epithelium does not tamely submit to the hyaline invasion, but as the hyaline separates the cells from their blood supply and finally forces them out of existence, growth occurs at the periphery of the island, particularly if adjacent to fat or fibrous tissue into which expansion can take place more readily than into the acinar tissue. However, encroachment on these new

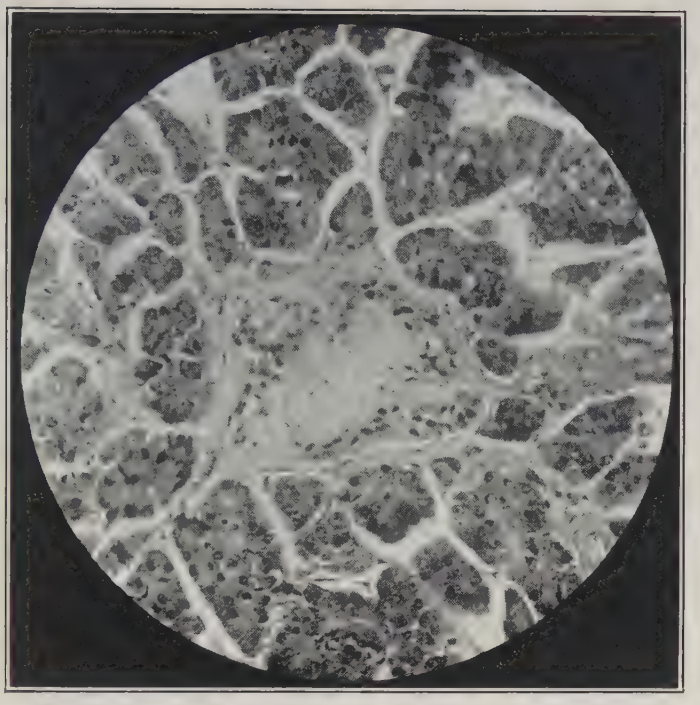

FIG. 6.—Moderate hyalinization of island of Langerhans. M979. Male, aged sixty-six years. Duration of diabetes fourteen years. This and the preceding figures are all taken from the same case showing the variation in hyalinization that may occur in the same pancreas. Eosin-methylene blue stain. × 170.

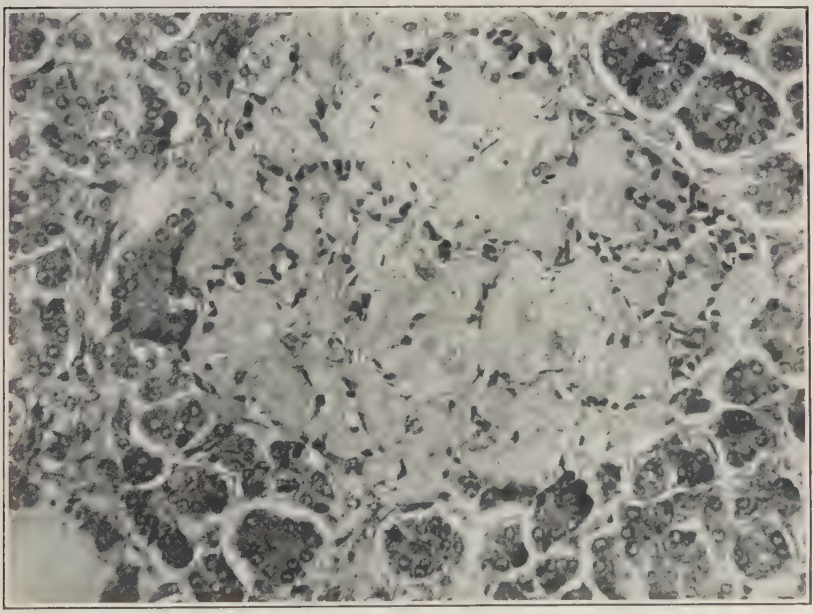

FIG. 7.—Marked hyalinization of island of Langerhans. DA27–95. Female, aged sixty years. Duration of diabetes five years. Note the few epithelial cells persisting at right hand margin of island. Mallory's aniline blue stain.

formed cells occurs, and finally results in the formation of very large hyaline masses, far larger than the original island. The end stage of such a process is shown in Fig. 8.

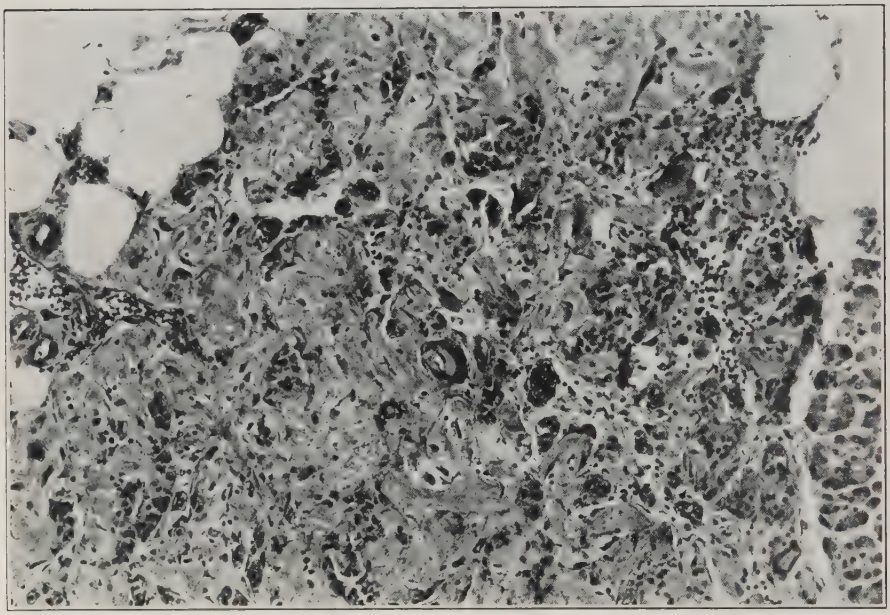

FIG. 8.—Pancreas. Large mass of hyaline material representing hyalinized island. Practically all epithelial cells destroyed. Note acinar tissue at right of figure, peripancreatic fat at left. No. 511. Male, aged seventy years. Duration of diabetes thirty-nine years. This mass is very many times the size of a normal island. Mallory's aniline blue stain. × 75.

TABLE 3.—HYALINE DEPOSITION IN THE ISLANDS OF LANGERHANS.

	Total number.	Number with hyaline.	Per cent with hyaline.
Cases under forty years of age	80	3	3.7
Cases over forty years of age	220	86	39.1
Cases under ten years' duration	209	58	27.7
Cases over ten years' duration	42	21	50.0

Even in the most marked case of hyalinization of the islands that I have ever seen, Mallory's A02-164, used for years as a class slide at the Harvard Medical School, rare uninvolved or nearly normal islands are present. This case was a male, aged forty-three years, whose diabetes was known to have existed for at least two years. Death occurred from coma in the course of pulmonary tuberculosis.

Rarely the hyaline becomes the seat of calcium deposition, so

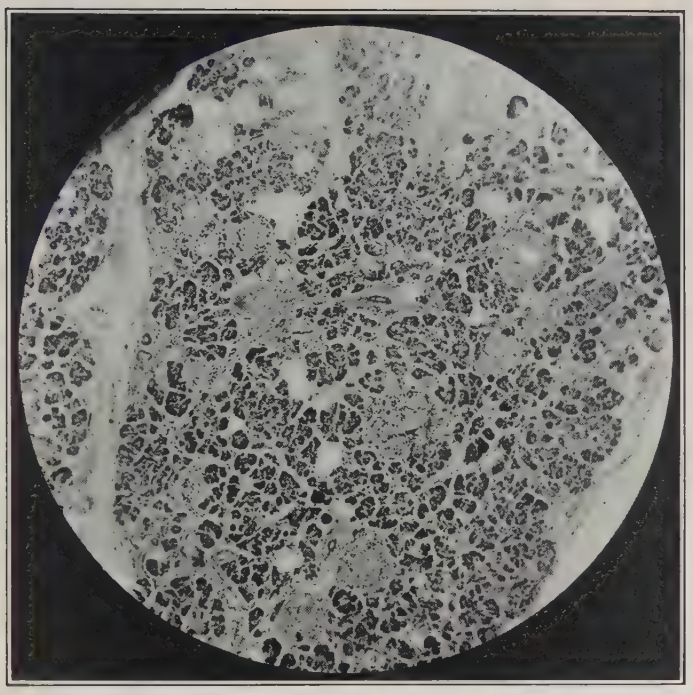

FIG. 9.—Pancreas showing large numbers of hyaline islands. U24–1. Female, aged forty-nine years. Duration of diabetes fifteen years.

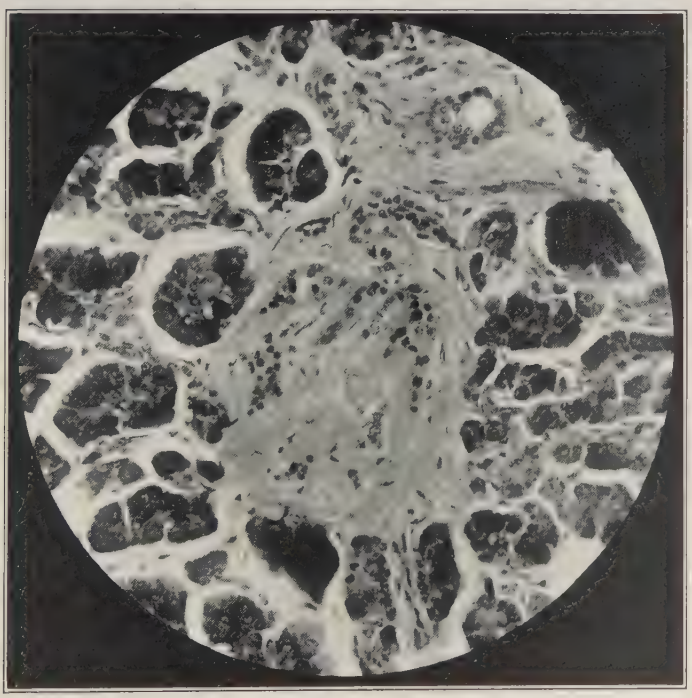

FIG. 10.—Extreme hyalinization of island of Langerhans. Note blood cells in still patent capillaries. M979. Male, aged sixty-six years. Diabetes of fourteen years' duration. Phosphotungstic acid hematoxylin stain. × 170.

that the pancreas may be studded with minute calcified nodules. One such case is described by Mallory,[4] and another by Gibb and Logan.[9] Escudero[10] states that calcification is extremely rare.

Hyalinization of the islands of Langerhans, in light of the foregoing evidence, may be considered as due to production of intercellular substance by fibroblasts and possibly by endothelial cells. When the process becomes sufficiently marked to destroy a number of the epithelial cells or to separate them from the blood stream by a practically impermeable membrane, diabetes will develop. It is of no slight interest that this pathological product usually appears in the later years of life, about the time that marked hyaline thickening of the small arterioles is prone to occur. The reason for the specific involvement of the islands, rather than the acinar tissue, is difficult to interpret, although the rich vascularity of the islands may provide a clue.

Diabetes associated with hyalinization of the islands is apt to be mild, due to the fact that there is relatively slow progress of the lesion and to the fact that almost always there is some evidence of uninvolved islands which may perhaps be considered as new formed, thus suggesting that in a slowly progressing lesion the pancreas is able for a time to prevent insulin deficiency through its regenerative ability.

TABLE 4.—LESIONS IN THE ISLANDS OF LANGERHANS IN 259 DIABETIC PANCREASES.

Age, yrs.	Cases.	Normal.	S+	S++	S+++	H+	H++	H+++	Hypertrophy.	Hydropic degeneration	Pyknotic nuclei.	Hemorrhage.	Adenoma.
0 to 10	10	2	0	0	0	1	0	0	0	2	2	0	0
11 to 20	23	10	4	0	0	0	0	0	0	1	0	0	0
21 to 30	20	7	3	2	1	0	1	0	2	2	1	0	0
31 to 40	21	9	3	3	0	0	1	0	0	3	0	1	0
41 to 50	34	9	3	6	1	0	5	7	4	2	0	0	0
51 to 60	63	15	11	5	1	1	15	14	7	2	1	0	0
61 to 70	63	12	6	6	3	5	17	14	5	2	0	0	1
71 to 80	19	2	6	1	1	1	0	6	2	1	1	1	0
81+	2	1	0	1	0	0	0	0	0	0	0	0	0
?	4	2	0	1	1	0	0	1	0	0	1	0	0
Total	259	69	36	25	8	8	39	42	20	15	6	2	1

S = fibrosis or sclerosis. H = hyaline.

Fibrosis.—The next most frequent change to hyalinization of the islands is fibrosis. According to Otani,[11] the normal island most commonly has no capsule. However, presence of a definite fibrous capsule is hardly enough evidence in itself to consider the island abnormal. In this series I have divided the islands showing fibrosis into three grades: (1) + Those showing a definite capsule with a moderate number of fibroblasts accompanying the capillaries within the island; (2) ++ a moderate degree of thickening of the fibrous

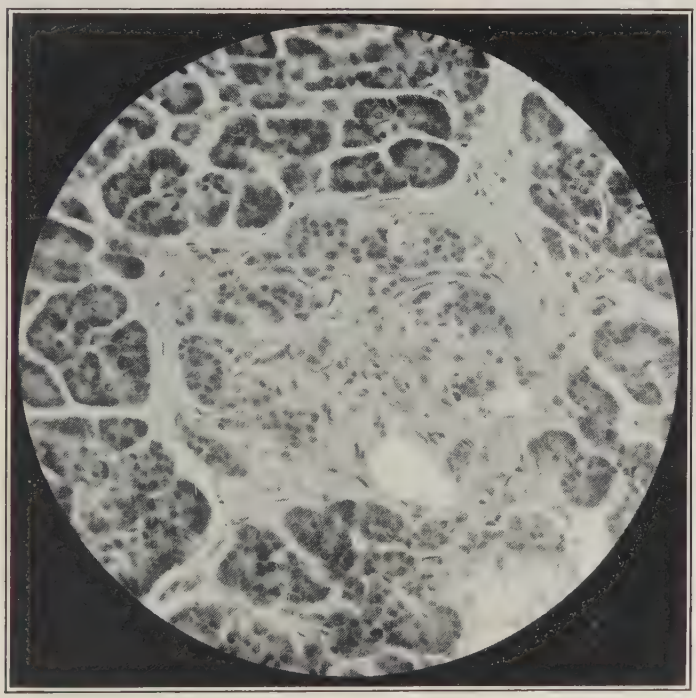

FIG. 11.—Fibrosis of island of Langerhans. U23–8. Aged fifty-nine years. Duration of diabetes seventeen years. Eosin-methylene blue stain. × 170.

capsule of the island and a large number of fibroblasts present about the capillaries within the island; and (3) +++ the more or less complete replacement of the islands by fibrous tissue scars. Slight fibrosis, or sclerosis as it is sometimes termed, is the most common, occurring in 36 cases. Moderate fibrosis occurred in 25, and marked fibrosis in 8. Thus a total of 69, or 27 per cent, of the pancreases in this series showed this type of change. Occasionally the same pancreas will show both hyalinization and fibrosis of its islands, and

in some even the same islands may show both lesions. Joslin's Case No. 1419, aged fifty-three years, whose diabetes had been present for 14.6 years showed extreme fatty infiltration of the pancreas with few islands. These show chiefly hyalinization, but some fibrosis was present as well. Death was due to acute appendicitis. Fibrosis, like hyalinization, tends to occur in older individuals. The fibroblastic proliferation begins at the capsule, and follows the vessels into the insular tissue. Not infrequently this change is associated

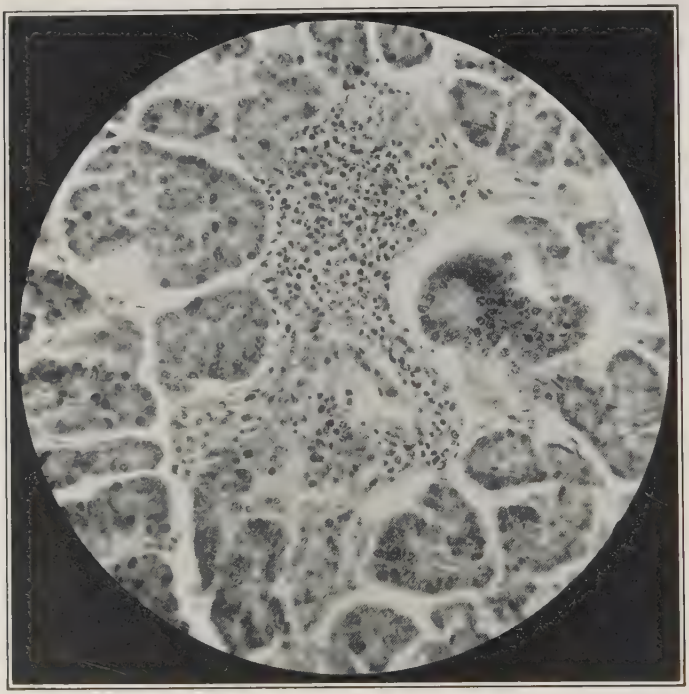

FIG. 12.—Marked lymphocytic infiltration and slight fibrosis replacing island of Langerhans. M942. Male, aged nineteen years. Duration of diabetes eleven months. Eosin-methylene blue stain. × 170.

with arteriosclerosis of the pancreatic vessels and it is practically always accompanied by interacinar or interlobular fibrosis.

Joslin's Case No. 3176, aged fifty-nine years, with diabetes of 17.3 years' duration, died from pulmonary tuberculosis. Autopsy showed marked sclerosis of the pancreatic vessels with hyaline thickening of the walls of the arterioles. The islands were markedly fibrosed, and the interacinar connective tissue was increased as well.

Lymphocytic Infiltration.—Certain of the cases, particularly in young persons, show lymphocytic infiltration[12] in and about the islands of Langerhans. Rarely the lymphocytes are accompanied by endothelial leukocytes. This type of change is particularly apt to be found in young individuals and in those with a relatively short duration of the disease. I associate this lesion with severe diabetes. Stansfield and I[13] reported one case, of interest owing to the peculiarly short duration and fulminating character of the diabetes, which developed in a girl, aged twelve years. She died in coma in spite of energetic insulin treatment five days after her diabetes was first discovered. The pancreas was small but reddened and swollen. Microscopic examination revealed numerous endothelial leukocytes and lymphocytes involving the islands. Of some interest from the speculative standpoint is the fact that she had been drinking unpasteurized milk from a cow with a severe case of garget. Other than the changes in the pancreas there was no pathology.

Another case is that of a boy, aged fifteen years, with onset of diabetes one year and seven months before death, which occurred in coma, several years before the discovery of insulin. The pancreas was small; the islands showed marked lymphocytic infiltration. Other than this and the typical abnormal glycogen distribution there were no pathological changes.

Hydropic Degeneration.—One of the diabetic lesions most difficult of comprehension from the pathological standpoint is hydropic degeneration, described by Weichselbaum,[14] and further emphasized by Allen.[15] On the basis of experimental work and clinical observations, Allen[15] regards this lesion of much importance on the following grounds:

"(A) Its presence affords a positive microscopic diagnosis of active diabetes.

"(B) It completes the proof of the island theory of diabetes.

"(C) It adds to the evidence of the essential identity of experimental and clinical diabetes.

"(D) It explains the permanent lowering of assimilation in diabetes consequent upon excessive diets.

"(E) From a broader physiological standpoint, it offers the only proved example of anatomical breakdown of cells due to overstimulation of an internal secretory function."

There has been no question from the early experiments of Allen[16] and of Homans[17] to the present time that hydropic degeneration is

an important lesion in experimental diabetes. There are so many factors to be considered in human diabetic material, however, that its interpretation is more questionable there.

The striking feature of hydropic degeneration is that it appears to be not the result of injury but of excessive functional strain. The bulk of intracellular reactions to injury, short of necrosis, are represented by the liberation of fatty or albuminous and related substances from the protoplasm, giving the pictures commonly described as fatty degeneration, albuminous degeneration or cloudy swelling, colloid degeneration, and so forth.

The typical hydropic degeneration is totally different from these. The specific granules disappear and are replaced by vacuoles, which grow and coalesce until the cytoplasm of the cell is apparently replaced by a watery fluid, leaving the nucleus alone in the embrace of the distended cell membrane. Apparently this change is reversible in its slighter degrees, but, once fully established, leads to the atrophy and disappearance of the cell involved. It is striking that this response to functional overstrain is unique among the endocrine glands and, indeed, among all the various organs. Perhaps the simplest physiological analogy to the pancreas in diabetes would be the thyroid in cases of myxedema, yet in the thyroid cells no such anatomical change develops.

It is rather difficult to explain all cases of hydropic degeneration on the basis of functional overstrain of the β cells. In going over this series of diabetic pancreases, I was struck by the frequent occurrence of appearances suggesting hydropic degeneration in many of the island cells of those pancreases removed over three hours postmortem, and the comparative rarity of this finding in pancreases removed one hour or less postmortem. Allen[18] believes that "hydropic degeneration is demonstrable in the human pancreas whenever diabetic symptoms have been sufficiently intense and prolonged but is ordinarily missed in the mildest cases." He also emphasizes the importance of fresh tissue for its demonstration. However, as pointed out by Conroy,[19] it is difficult to see how a cell with cytoplasm practically replaced by vacuolization, or by one large vacuole, could through postmortem change acquire normal appearing cytoplasm.

The relation to duration of the diabetes is somewhat uncertain, but the most striking cases of hydropic degeneration which I have seen have been in fulminating cases of diabetes of relatively short duration. I am indebted to Dr. John R. Williams for the privilege

of studying the pancreas of one case of only three weeks' duration which showed marked hydropic degeneration. Several of my cases of diabetic children with severe diabetes progressing rapidly to coma showed suggestive changes, but postmortem change could not be ruled out.

Allen[18] also considers that the pathology of diabetes indicates "the diabetic pancreas represents in most cases a burned-out conflagration and the chief or sole cause of aggravation of the condition lies in hydropic degeneration of the islands."* This presupposes in the average case of severe diabetes that the hydropic degeneration remains as a prolonged phase of cellular pathology, a conception without parallel in degenerative processes. It is difficult to see how a cell so damaged as to have lost its function, and to appear on the verge of dissolution, could persist without further change in this presumably labile state for long periods. The only other alternative is to assume that island cells have undergone hydropic degeneration, disappeared, and new island cells been formed at a rapid rate to take their place, only in turn to undergo degenerative change. This dynamic explanation may be correct, but the cycle would have to proceed at a rapid pace that should show far more evidences of regeneration than are usually encountered.

Nevertheless, the pathology of diabetes must be considered as dynamic, not static.

It may be objected that the rarity of hydropic degeneration in my series (only 15 cases) is due to the large number of insulin-treated cases on the theory that insulin, by reducing functional strain, reduces the frequency of the lesion.

If Allen's statement holds that the chief cause of aggravation of diabetes lies in hydropic degeneration of the islands, this is of great importance, for if the above interpretation can be put on my observations, insulin treatment seems to have prevented the development of this lesion. Of course, it should do this, provided the blood-sugar is kept at normal level, if we accept functional overstrain as the cause of this degeneration. Assigning to hydropic degeneration such an important rôle, and finding the change absent in insulin-treated cases, the implication is that such cases should not lose tolerance. However, the change is nearly as rare in my cases not given insulin (some dying before the Banting Era, some during it) as in those treated with insulin.

I have seen pancreases from pre-insulin cases of diabetes of short

* A further consideration of this statement will be found in Chapter XVIII.

duration dying in coma, and pancreases from mild diabetics dying from arteriosclerosis or intercurrent infection after twenty-five or thirty years of diabetes, and neither group showing evidence of hydropic degeneration. Two cases of apparent hydropic degeneration were encountered in my control series, and the histories of both, when carefully studied, gave no evidence of diabetes.

In no case of the series reported by Root and myself[20] was hydropic degeneration positively diagnosed. Conroy,[19] before the days of insulin, found hydropic degeneration in only 1 of 12 diabetic pancreases exhaustively studied.

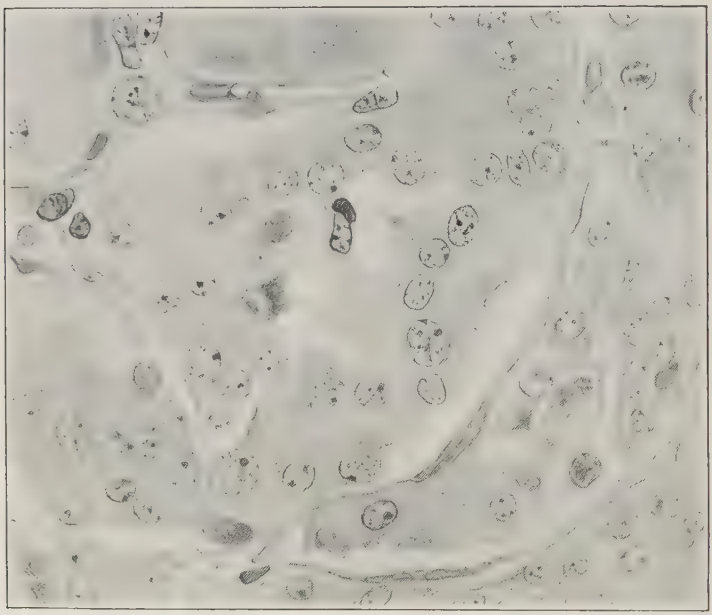

FIG. 13.—Pancreas showing apparent hydropic degeneration. Note extreme vacuolization and frayed-out appearance of many of the island cells. This appearance was produced by leaving the pancreas at room temperature. No. 86. Four hours postmortem. Female, aged eighty-four years. Non-diabetic. Goodpasture's polychrome methylene blue stain. × 800.

While the existence of hydropic degeneration as a clear-cut lesion in experimental animals and human diabetics is unquestionable, nevertheless it can be very closely simulated by postmortem change. Such a case is well shown in Fig. 13. Several times I have succeeded in producing apparent hydropic degeneration by the simple expedient of leaving a portion of normal pancreas at room temperature

for eight or ten hours before fixation. The lapse of many hours between death and autopsy in most of Weichselbaum's cases may have some bearing on the frequency with which he found the lesion.

Pyknotic Nuclei.—One appearance in the islands which is interpreted only with considerable difficulty is the presence of pyknotic nuclei and somewhat shrunken cells. Occasionally islands are found closely resembling normal except for the presence of extreme pyknosis of the nuclei and acidophilic cytoplasm. I have encountered this change in 6 cases. These cases ordinarily show no other lesion in the islands, if indeed this nuclear change may be considered a lesion. One cannot help but feel that it may be either postmortem change or improper fixation that produces these shrunken, extremely dense nuclei. However, cases autopsied soon after death and showing no evidence of postmortem change, do show these pyknotic nuclei in the island cells. Gibb and Logan[9] encountered these islands in 15 cases among 142.

Hypertrophy.—Hypertrophy of the islands is not infrequently encountered. Cecil[21,22] has pointed out two types of hypertrophy of the islands—one a simple increase in size of the island without change in the character of the individual cells; the other a change in the cells to a columnar type with the nuclei located centrally. Rudimentary islands of this latter type Weichselbaum[23] encountered in 19 cases of diabetes out of 151, and regarded them as representing regeneration of islands from duct epithelium. Cecil agrees that this type of hypertrophy is seen in islands newly formed from duct epithelium. He found 34 cases of hypertrophy and probable regeneration in 100 diabetic autopsies, none in 33 cases of chronic pancreatitis, and only 1 in 17 cases of carcinomatous involvement of the pancreas.

The two types of hypertrophy are easily distinguished. The coiling, snake-like columns of cells in the islands are quite different in appearance from the typical sinusoidal structure, although the close relation of cells and vessels is maintained. The epithelial cells themselves are somewhat changed, tending toward a columnar rather than the usual cuboidal polyhedral shape. Irregular projections among the acini at the periphery of the island are common. This change appears to have no definite correlation with the pathological physiology.

Twenty cases in this series showed a greater or less degree of hypertrophy of the islands of Langerhans. Usually not all the islands are hypertrophied but only a moderate proportion of them.

However, occasionally the majority may appear much enlarged. Islands were considered hypertrophic when they measured more than 400 micra in diameter. There is no correlation between the occurrence of hypertrophy, the age of the patient, the duration of the diabetes or the severity of the diabetes. In one instance markedly hypertrophic islands were present in the tail of a pancreas from which practically all acini had disappeared secondary to car-

FIG. 14.—Hypertrophy of island of Langerhans. A09–6. Non-diabetic. Eosin-methylene blue stain. × 40.

cinoma of the head of the pancreas. Diabetes had developed ten years before death and was easily controlled for the first seven years. Then the case became more or less insulin resistant and symptoms referable to the tumor became increasingly prominent.

Hemorrhage. Hemorrhage into the islands has been described, but is probably either a postmortem change or an artefact, as a glance at Fig. 15 suggests. In only 2 cases was this hemorrhagic change at all noticeable, and in one of these a man, aged seventy-two

years, with diabetes of twenty-two years' duration, cardiac decompensation was the cause of death, with extreme passive congestion.

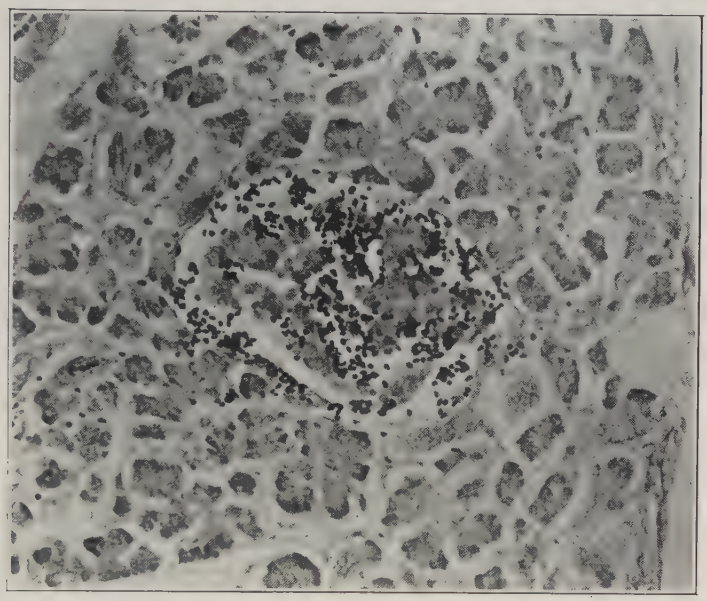

FIG. 15.—Postmortem change simulating hemorrhage into island of Langerhans. No. 1638. Male, aged sixty-eight years. Non-diabetic.

Adenoma. Adenoma of the islands of Langerhans was encountered only once in this series, in a case of a male, aged sixty-seven years, whose diabetes was of unknown duration. The cause of death was mesenteric thrombosis. The pancreas weighed 130 grams. On microscopic examination it showed a moderate degree of fibrosis of the interacinar type and a marked degree of fatty infiltration. The islands were normal in number and showed a moderate degree of fibrosis. At one margin of the pancreatic tissue was a rounded, encapsulated nodule compressing the adjacent tissue. On microscopic section this nodule was seen to be made up of cells similar to those of the islands and its structure similar to that of the islands.

Among the series of adenomas of the islands of Langerhans I[24] reviewed recently there is only one, that of Heiberg,[25] which occurred in a diabetic. Here there was a large mass of insular tissue, 6 by 5 mm. in diameter, which was found in the pancreas of a white female, aged sixty-four years, dying in diabetic coma.

FIG. 16.—Small adenoma of island of Langerhans. Note capsule and compression of surrounding tissue. H26–177. Female, aged fifty-three years. Non-diabetic. Mallory's aniline blue stain. × 40.

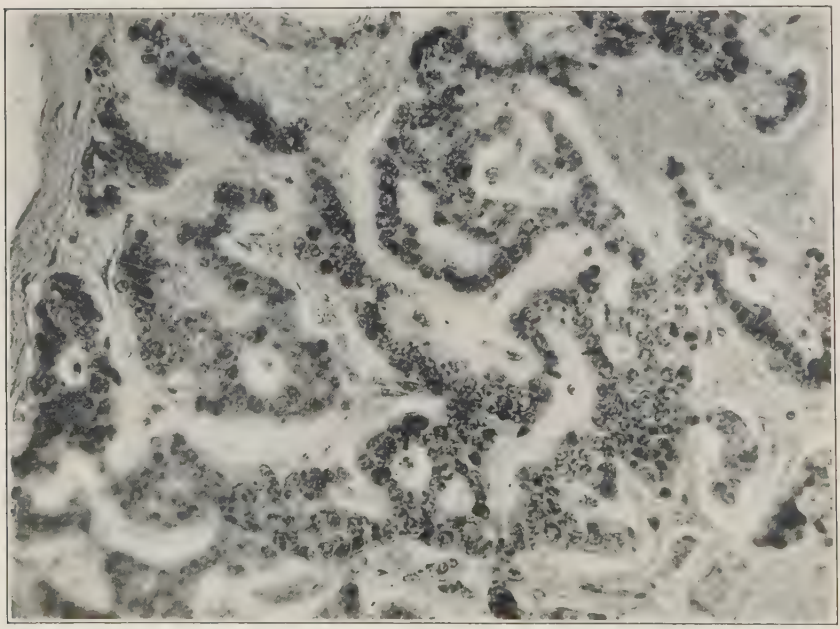

FIG. 17.—Adenoma of island of Langerhans. A09–101. Female, aged forty-eight years. Non-diabetic. Mallory's aniline blue stain. × 200.

Islands Apparently Normal. Of particular importance from the theoretical as well as practical standpoint is the fact that a considerable portion of diabetic persons show no demonstrable pathology in the islands of Langerhans. Out of the 259 pancreases available for detailed study among the 300 diabetic autopsies in this series, 69, or 27 per cent, showed islands which were normal so far as could be determined by histological means. A considerable proportion of these normal islands occurred in insulin-treated cases that possibly might have shown hydropic degeneration if they had not been so treated. However, a very fair number occurred in pre-insulin days, or in cases which had received no or inadequate insulin.

The existence of these normal islands in diabetes mellitus has long been a puzzle to pathologists. It is rather difficult to conceive how we can have an insular diabetes with normal islands of Langerhans present, particularly a disease that persists as long as life itself. This leads to one of three hypotheses: (1) The islands may be normal and insulin may be produced, but is either defective in quality or is neutralized by some substance in the body; (2) the diabetes may be of other than insular origin; (3) the insulin may be formed normally by normal islands, but through failure in transport the insulin is not brought into the blood stream and so not distributed to where its effects are needed. Whichever (if any) one of these hypotheses is true, we must face the fact that cases of diabetes absolutely identical with one another from the clinical standpoint show no evidence of structural disease in the islands of Langerhans in one instance, and show marked injury of various types in still another.

Fatty Infiltration.—One minor change concerning the importance of which there has been a good deal of discussion is the presence of fat in the island cells. This was first pointed out by Dogiel.[26] In many cases of diabetes this can be demonstrated by either osmic acid or Sudan III or IV in many of the island cells, usually in considerably greater degree in the islands than is present in the acinar tissue. In sections stained with Sudan IV the islands may appear under low magnification as definitely orange spots. At one time this was considered to be a specific change characteristic of diabetes. Weichselbaum and Stangl[27] found in their material that diabetics showed more fat in the islands of Langerhans at autopsy than did those dying at the same ages from other disease conditions. The work of Symmers[28] showed that the presence of fat in the islands

was not characteristic of diabetes, but was present in other diseases, notably alcoholic intoxication in which it was particularly prominent. In fact, Symmers felt the lesion was to some extent characteristic of prolonged alcoholic intoxication.

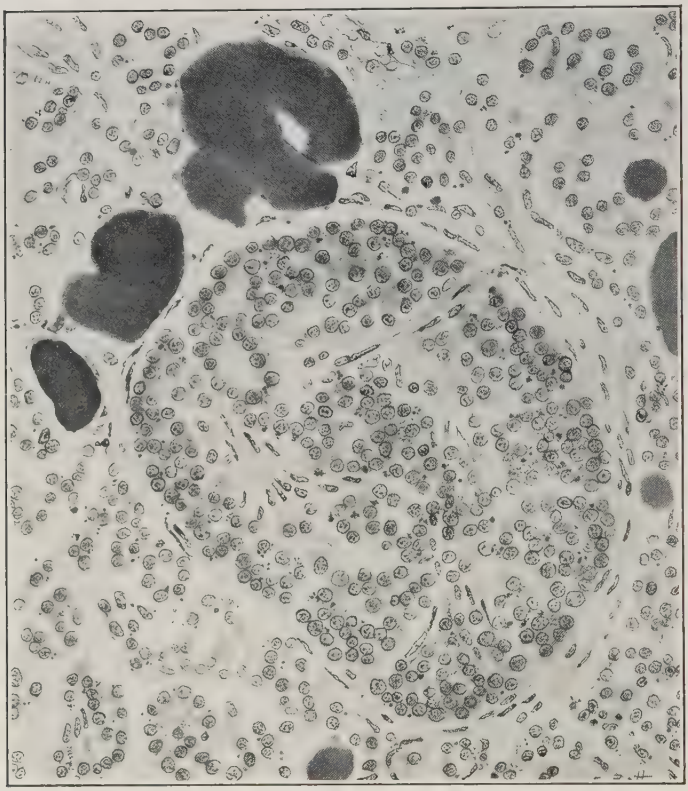

FIG. 18.—Pancreas showing lipomatosis and moderate fatty infiltration of island epithelium. DA26–35. Female, aged fifty-four years. Duration of diabetes five years. Sudan IV stain. × 310.

Wilder[29] felt that this lesion, if it can be called such, although more frequent in diabetic than in non-diabetic persons, was probably a result rather than cause of diabetes. In its most striking form, the islands appear in Sudan-stained sections as deep orange-red spots. Wilder found marked fatty infiltration in 11 cases, moderate in 15. Table 5 shows the degree of fatty infiltration in a number of pancreases from my series, both diabetic and non-diabetic.

TABLE 5.—FAT IN THE ISLANDS OF LANGERHANS.

	Degree of infiltration.		
	Slight.	Moderate.	Severe.
Diabetic cases	0	18	13
Non-diabetic cases	1	2	6

Apparently there is no significance to be attached to this lesion. An example of moderate infiltration is shown in Fig. 18.

TABLE 6.—QUALITATIVE INSULAR CHANGES IN DIABETES MELLITUS.

Author.	Total cases.	Normal.	Hyaline.	Fibrosis.	Hydropic degeneration	Pyknotic nuclei.	Hemochromatosis.	Lymphocytic infiltration.	Hypertrophy.
Cecil[21]	90	0	27	49	0	0	2	1	41
Wilder*[29] . . .	29	8	4	12	0	0	0	5	0
Gibb and Logan[9] .	142	11	30	79	0	15	7	0	0
Warren	259	69	89	69	15†	6	3	9	20
Total . . .	520	88	150	209	15	21	12	15	61

* Only those of Wilder's cases are included in which the pancreas was specifically described.

† The benefit of the doubt has been given this lesion. In not over 6 cases is it absolutely definite.

QUANTITATIVE VARIATIONS IN THE ISLANDS OF LANGERHANS.

Enumerating the islands in the human pancreas is extremely difficult and for practical purposes only rough estimates are possible, based on the total number of islands in a number of representative sections taken from different portions of the gland. Any method such as this, of course, is exposed to numerous errors and presumably the statements as to the number of islands occurring in a given human pancreas are all open to question. The methods worked out by Bensley[30] and his students for enumeration of the islands in experimental animals are extremely valuable there, but are rarely applicable to human tissues. Clark,[31] working in Bensley's laboratory, was able to count fairly accurately the number of islands in the pancreas of several human adults. He found the number to range from 250,000 to 1,750,000.

In the diabetic pancreases which I have studied, the number of islands has been estimated from those encountered in a considerable

number of sections taken from various portions of the gland. I have attempted no exact enumeration in this series, but when there has been considerable difficulty in finding the islands as compared with sections of normal pancreas I have noted them as "few."

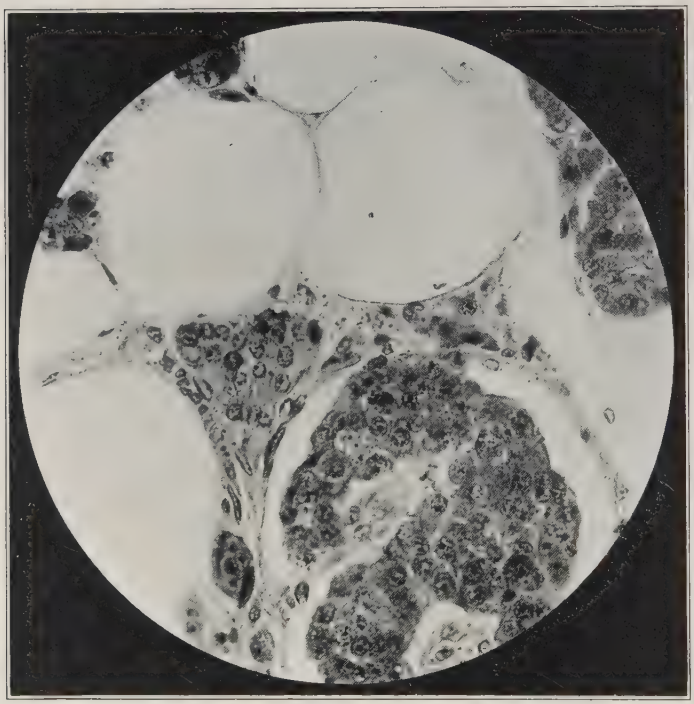

FIG. 19.—Mitosis in island cell. Death from lobar pneumonia. A15–16. Non-diabetic. Mallory's aniline blue stain. × 425.

In this series of 259 pancreases from diabetic individuals available for detailed microscopic study, 51 showed an apparent decrease in the number of islands. However, until methods more readily applicable to human tissue than those at present available are evolved, the problem of quantitative determination of the number of islands is too vague to warrant detailed discussion.

Changes Involving the Pancreas as a Whole.—Aside from the insular changes, changes in the pancreas as a whole must be considered, particularly those involving the acinar cells. Fibrosis is perhaps the simplest and most frequently occurring change. Normally there is only a relatively delicate fibrous tissue septum between the

lobules of the pancreas, and there is a delicate basement membrane rarely more than one cell thick between the acini and the islands. Fibrosis, both interlobular and interacinar, is not infrequent. It may or may not be accompanied by a moderate degree of round-cell infiltration, either lymphocytes or endothelial leukocytes. This change may vary from irregular patches of fibrous tissue scattered through the pancreatic substance, often tending to center about the ducts, to the almost complete disappearance of the acinar tissue with dilatation of the ducts characteristic of obstruction, such as one sees in ligation experiments.

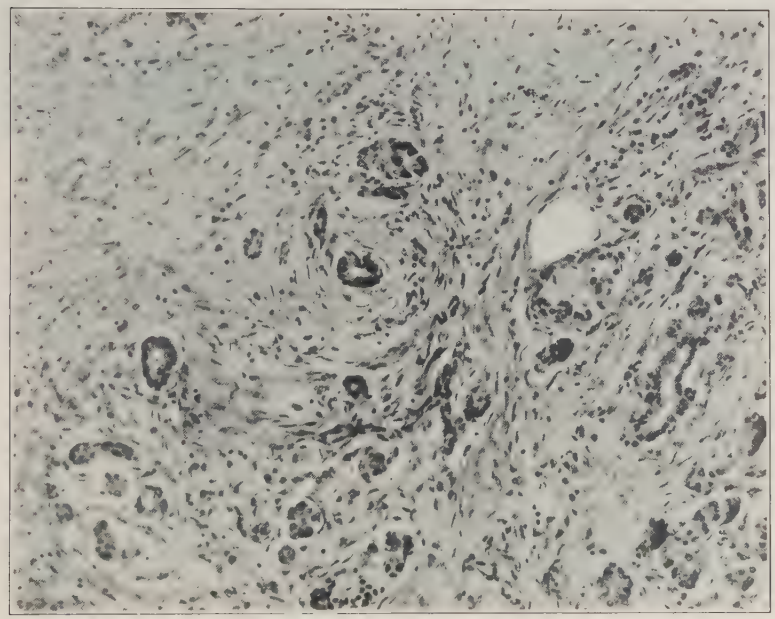

FIG. 20.—Marked fibrosis of pancreas, both interlobular and interacinar. No. 511. Male, aged seventy years. Duration of diabetes thirty-nine years.

Of the 155 cases that showed varying degrees of fibrosis, 51 showed slight fibrosis, the bulk of which was interacinar, 77 showed moderate fibrosis, again the bulk of which was interacinar rather than interlobular, and 27 showed marked fibrosis, again predominantly of the interacinar type.

There is no definite relationship between the occurrence of island lesions and interacinar fibrosis. However, I have never seen a

severe case of either hyalinization or fibrosis of the islands that did not show at least a moderate degree of interacinar fibrosis.

Lipomatosis.—Fatty infiltration or lipomatosis of the pancreas as a whole has been considered as characteristic of diabetes. In Fig. 21 is shown the extreme degree of fatty infiltration which can occur in a pancreas. Here hardly any epithelial tissue remains, the organ being converted into little more than a mass of fat and fibrous tissue. The amount of pancreatic fat is very closely related with that of the normal body fat and probably represents simply the degree of fat storage rather than being associated with the diabetic process

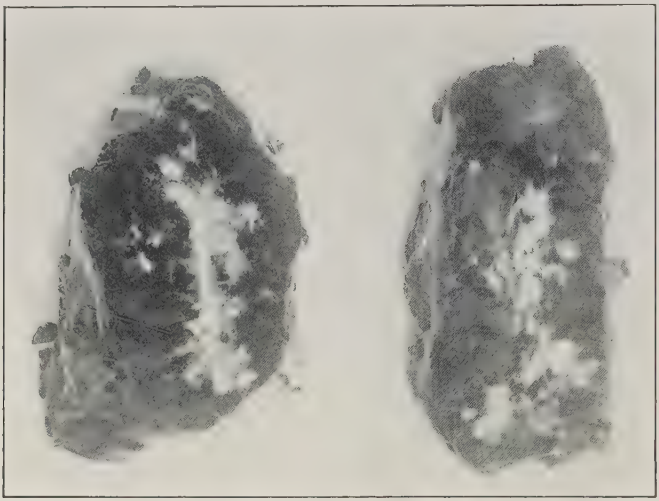

FIG. 21.—Extreme lipomatosis of pancreas. Note white epithelial tissue imbedded in large mass of fat. Fat has been stained with Sudan IV to provide better contrast. No. 1890. Female, aged sixty-five years. Duration of diabetes eight months. Natural size.

in any peculiar way. Sixty-nine, or 27 per cent, of the cases in my series showed varying degrees of lipomatosis, ranging from a slight deposit of fat among the acini and along the interlobular septa, to an extremely marked riddling of the pancreas with large and small deposits of fat, frequently occurring in single cells.

Arteriosclerosis.—Marked sclerosis of the pancreatic vessels occurred in 15 cases. Arteriosclerosis of the pancreas is not nearly so common as is arteriosclerosis of the spleen, which lies in the same vascular circuit. While the splenic artery may be extremely sclerosed and calcified, tortuous, there frequently is relatively little

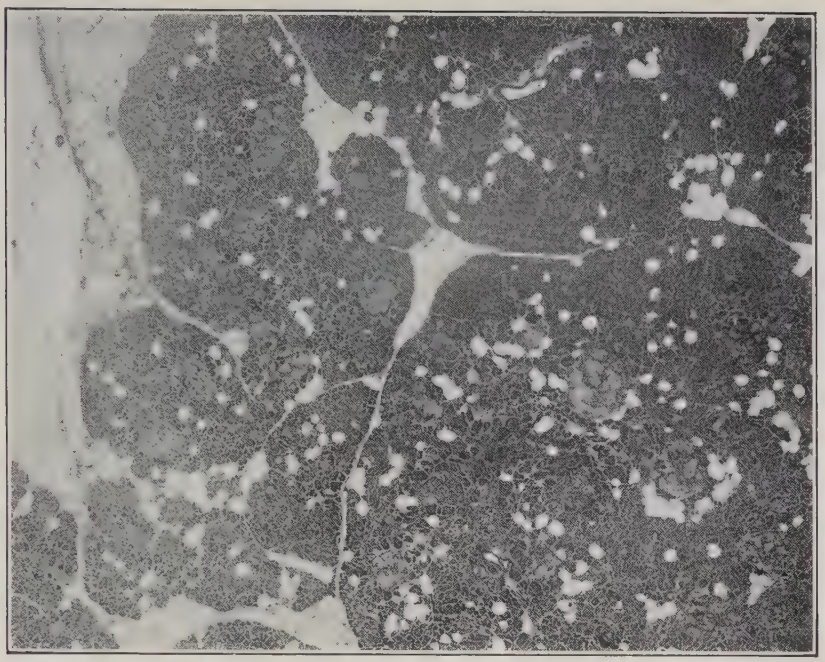

FIG. 22.—Lipomatosis. DA27–95. Female, aged sixty years. Duration of diabetes five years. Note large amount of perilobular fat and scattered fat cells throughout acinar tissue. Note also large number of hyaline islands. Phosphotungstic acid hematoxylin stain. × 22.5.

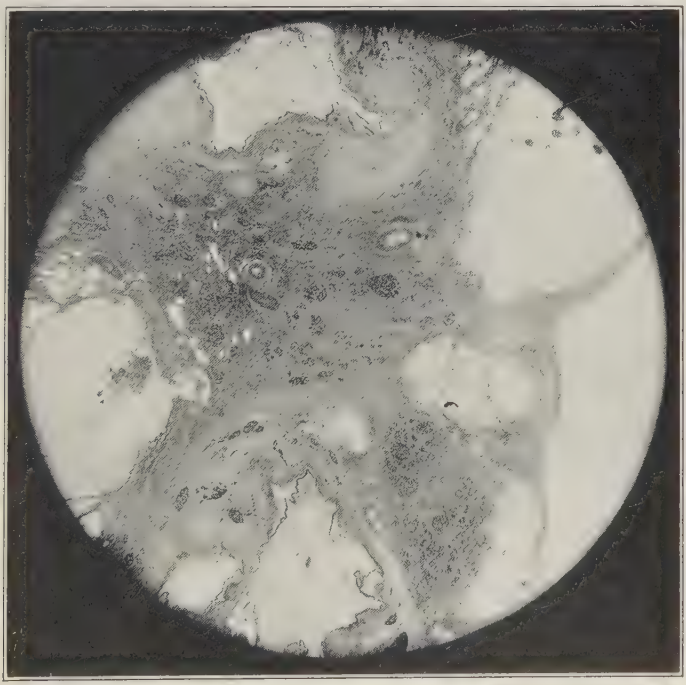

FIG. 23.—Marked fibrosis and lipomatosis of pancreas with practical disappearance of acinar tissue. Note marked dilatation of ducts and large number of islands present in the fibrous tissue. Change secondary to carcinoma of the head of the pancreas. U24–33. Female, aged sixty-nine years. Duration of diabetes eleven years. Eosin-methylene blue stain. × 15.

change in its branches which lead to the pancreas and there frequently is very little change in the pancreatico-duodenal artery. With only 5 per cent of the pancreases showing a marked degree of arteriosclerosis, arteriosclerosis as a factor in the production of diabetes while it cannot be ruled out is hardly of outstanding importance.

FIG. 24.—Pancreas showing marked fibrosis and lipomatosis. Note mucous glands in left lower corner. A22–118. Non-diabetic. Eosin-methylene blue stain. × 15.

Pancreatitis.—Acute pancreatitis appeared in 6 cases of this series. Three additional cases showed subacute pancreatitis as indicated by the presence of localized fat necroses or of localized necrosis of epithelial cells, with a certain amount of eosinophilic and polymorphonuclear leukocytic infiltration. In the acute cases the diabetes had developed after the onset of symptoms of acute pancreatitis, so here we have the development of diabetes simply through destruction of a considerable proportion of the pancreatic tissue just as one might surgically remove a sufficient amount of the pancreas to cause the development of diabetes experimentally.

Probably cases of diabetes after acute pancreatitis would be more

frequent were it not that the lesions which destroy enough of the pancreas to produce insulin deficiency are generally sufficiently severe to cause death from the pancreatitis itself, before there had been opportunity for diabetes to demonstrate itself.

FIG. 25.—Longitudinal section of pancreas from case of acute hemorrhagic pancreatitis. Note white fat necroses. No. 537. Male, aged seventy-one years. Non-diabetic.

FIG. 26.—Section through head of pancreas from same case as Fig. 25 showing marked necrosis and hemorrhage. Natural size.

The subacute cases probably represent only minor changes occurring in the pancreas subsequent to the diabetes, and they are probably not in any way associated with the diabetic process.

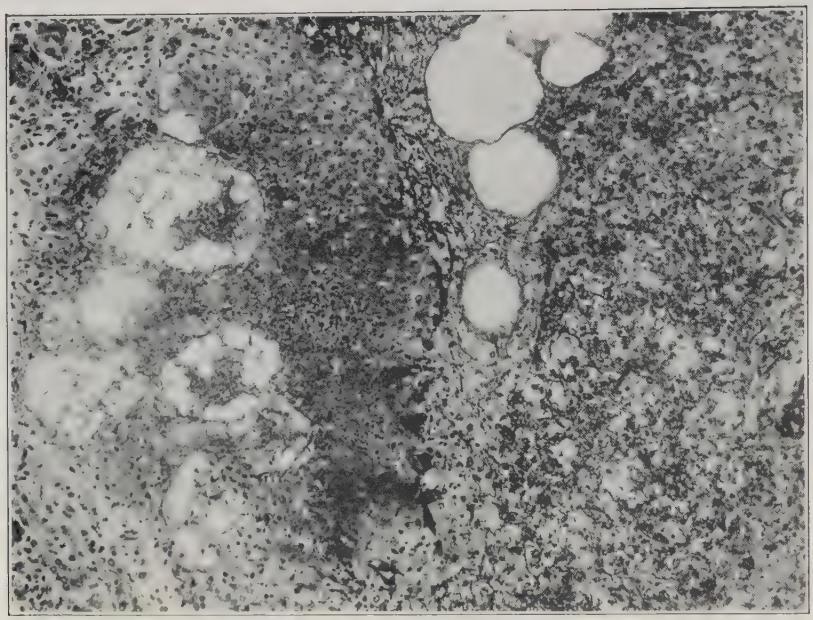

FIG. 27.—Acute pancreatitis showing necrosis of pancreatic tissue, fat necrosis, fibrin deposits, and leukocytic infiltration. No. 537. Male, aged seventy-one years. Non-diabetic. Iron hematoxylin-Van Gieson stain. × 150.

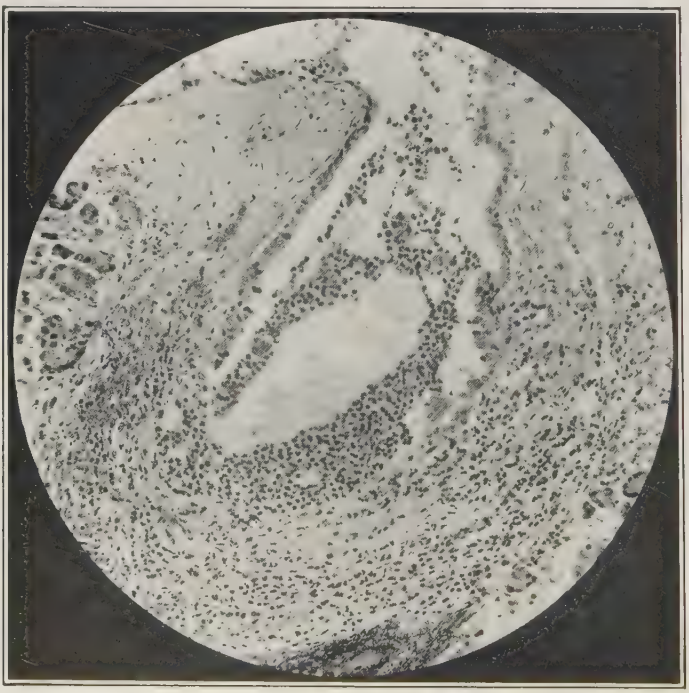

FIG. 28.—Acute pancreatitis, periductal. Note polymorphonuclear leukocytes within ducts and infiltration of wall. A14–79. Eosin-methylene blue stain. × 110.

Warfield[32] has summarized the available information on the relation of pancreatitis to diabetes, reporting a total of 11 cases, 7 of which were collected from the literature.

Abscesses.—Four cases of metastatic abscesses in the pancreas were encountered, all in persons suffering from staphylococcus pyemia.

Calculi.—In my series of 300 autopsied diabetics pancreatic calculi were encountered three times. Wilder[29] reported 3 cases among 55 autopsied cases. One of his cases showed hemochromatosis also, another gall stones and the third cholecystitis. Morrison and Bogan[33] have pointed out that the diagnosis can be made during life by Roentgen-ray. Fig. 33, taken from one of their plates, shows multiple calculi in a diabetic girl, aged twenty-three years. They reported 8 cases, of which 4 were diabetic.

The presence of calculi naturally predisposes to fibrosis of the pancreatic tissue, either through direct obstruction or tendency to localized infections with subsequent scarring. In obstruction the effect is closely akin to that of duct ligation, resulting in atrophy of the acinar tissue and persistence, at least for a considerable time, of the islands. This lesion is of much historical interest, as 1 case, reported by Barron,[34] aroused Banting's interest, and thus played a part in the development of insulin.

Case DA27-1, an obese white woman, aged seventy-four years, died of pulmonary embolism after a thigh amputation. Diabetes had been present for at least ten years. The pancreas weighed 30 grams, showed many small cysts due to local dilatation of the ducts and a small calculus in the duct. The islands showed marked hyaline change and moderate fibrosis. The pancreatic vessels were so markedly sclerosed that actual bone formation had occurred in the wall of one artery. There were many cholesterol stones in the gall bladder.

Case A25-154, a white woman, aged sixty-two years, died from carcinoma of the uterus after diabetes of two years' duration. The pancreas was normal in size and contained scattered concretions in the ducts. The islands showed moderate hyaline change. The gall bladder was negative.

Case No. 1020, a white male, aged fifty-one years, died of staphylococcus septicemia secondary to a carbuncle. Diabetes had been present for twenty-three years. The pancreas weighed 95 grams. There were scattered calculi in the ducts. The islands showed marked hyaline change. The gall bladder was negative.

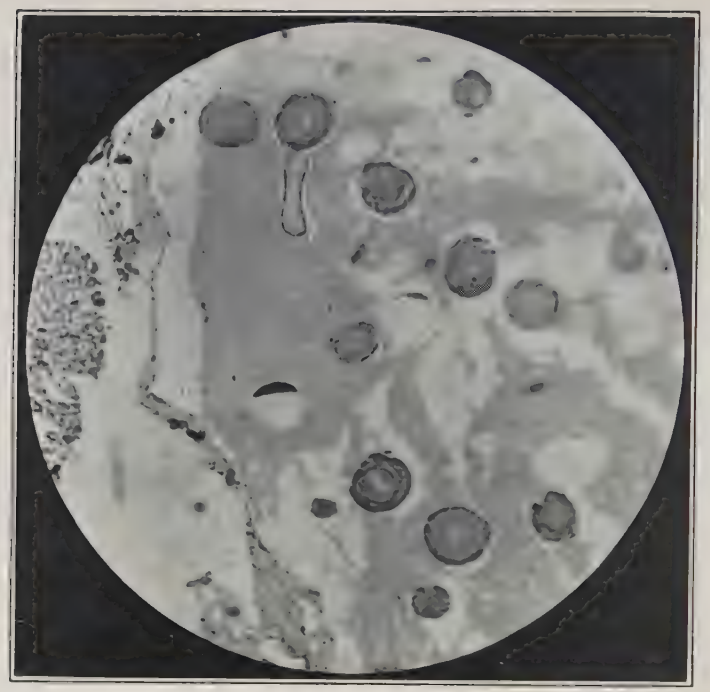

FIG. 29.—Pancreatic cysts with concretions. A17–62. Non-diabetic. × 22.5.

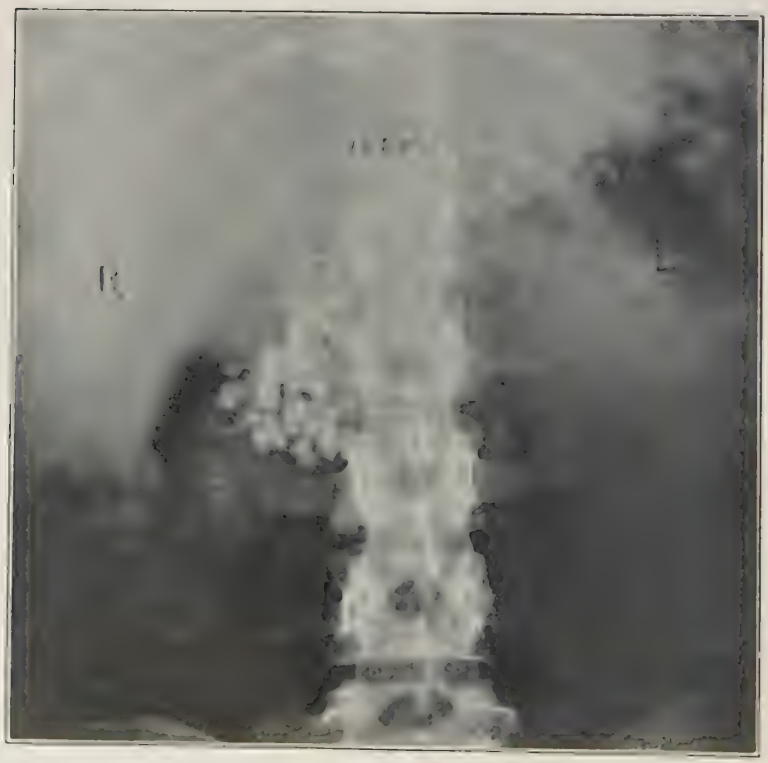

FIG. 30.—Roentgen-ray showing pancreatic calculi. Female, aged twenty-three years. Duration of diabetes five years. (Morrison and Bogan, New England Journal of Medicine.)

Amyloidosis.—Since reactions characteristic of amyloid were not infrequently obtained in cases of hyalinization of the islands, I was much interested in the occurrence of amyloidosis. This was found in only 2 cases. One, a female, aged sixty-two years, died of carcinoma of the uterus, with diabetes of two years' duration. Calculi were also present in the pancreas. The other, a female, aged fifty-four years, whose diabetes had been present for 4.9 years, died of multiple abscesses and staphylococcus pyemia.

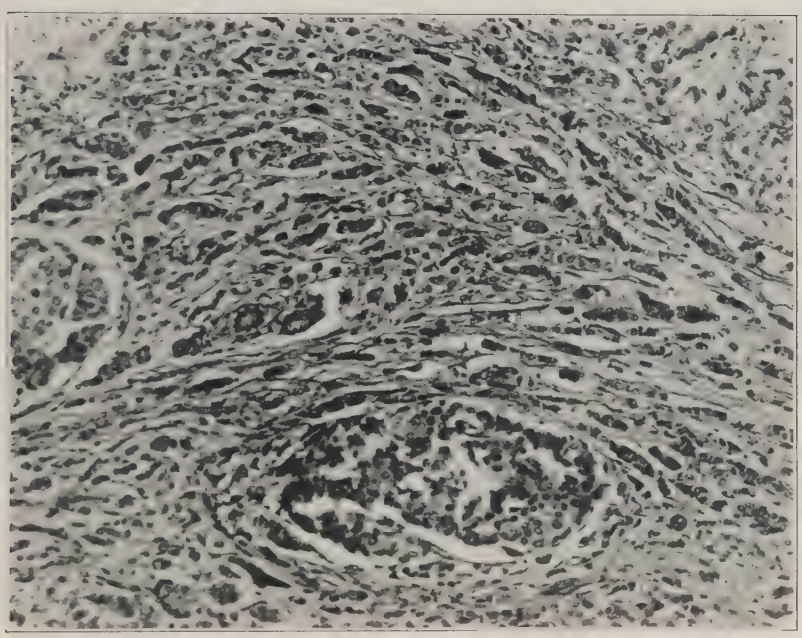

FIG. 31.—Carcinoma of pancreas showing persistence of islands in the midst of tumor tissue. No. 1638. Male, aged sixty-eight years. Non-diabetic. Phosphotungstic acid hematoxylin stain. × 190.

Carcinoma.—While carcinoma is of relatively infrequent occurrence among diabetics (66 fatal cases among 1756 diabetic deaths reported by Joslin[35]), carcinoma of the pancreas is not a rare lesion compared with other types of carcinoma. Whereas the average incidence of carcinoma of the pancreas is only 4 per cent out of all malignant tumors, it was found by McKittrick and Root[36] in 32.4 per cent of the 37 cases of malignant disease in diabetics seen at the New England Deaconess Hospital during three and a half years from 1923. In this series only 2 cases of carcinoma of the pancreas

(16.6 per cent of the total cases of malignancy) were encountered, although perhaps one additional case may be added inasmuch as it was impossible from either gross or microscopic examination to determine whether it arose from the common bile duct or from the pancreatic duct. In the series of carcinomas of the pancreas reported by Kiefer,[37] from the Peter Bent Brigham Hospital, diabetes was not a factor. We may conclude that carcinoma of the pancreas is no more common in diabetic than in non-diabetic individuals. On the other hand, compared with the other tumors occurring in diabetics, it is very frequently met with.

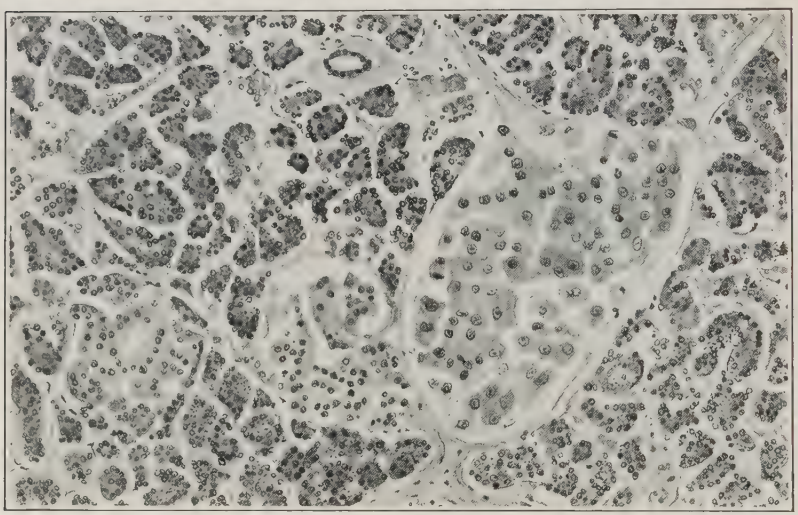

FIG. 32.—Carcinoma of island-cell type simulating appearance of islands of Langerhans. Eosin-methylene blue stain. × 250.

Metastatic tumors involved the pancreas in 2 instances, one, the questionable case of carcinoma of the gall bladder or carcinoma of the pancreas mentioned above, the other a carcinoma of the ovary with multiple metastases.

In this series of 300 autopsied cases of diabetes, 220 of which were over forty years of age, and hence in the age group most susceptible to cancer, there were only 12 cases of malignant disease. Since closing the tables, 1 additional case in a diabetic, an acute myelogenous leukemia, has come to autopsy.

Quantitative Variations.—So far as the size of the pancreas itself is concerned, there is relatively little indication one way or another

as to the rôle that this plays. Of the 229 cases in which the weight of the pancreas was known, there were 53 cases in which the pancreas was noted as definitely small or less than 50 grams, 141 cases in which the pancreas was normal or between 50 and 100 grams and 35 cases in which the pancreas was large, over 100 grams. Of course the weight must be accepted with more than a grain of salt as the degree of fatty infiltration can only be estimated and a pancreas, for example, may weigh as much as 240 grams and yet contain less pancreatic tissue than one weighing perhaps 50 grams.

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CHAPTER IV.

LESIONS OF THE PANCREAS IN NON-DIABETIC INDIVIDUALS.

To serve as a control for the lesions of the pancreas in cases of diabetes, discussed in the last chapter, the pancreas was studied in 200 consecutive autopsies performed on non-diabetic individuals in this laboratory in 1928 and a portion of 1929. The findings in the first 156 of these have already been reported.[1] The primary cause of death ranged from such chronic conditions as carcinoma, multiple sclerosis and endocarditis to pneumonia, meningitis and postoperative pulmonary embolus. These cases are fairly representative of various ages, ranging from one day to eighty-seven years, at the time of death. However, as may be seen from the tables, they are rather weighted in the later decades. Thus the age distribution is not unlike that of diabetic deaths. In only 6 cases were pancreatic changes an important factor in the clinical course or the causation of death.

So much attention has been paid to even minor lesions in the pancreas of diabetics, without much regard to changes seen in the pancreas of non-diabetics, that a tendency has developed to relate complacently almost any type of pancreatic lesion with diabetes.

Methods.—Sections of the pancreas were fixed routinely in Zenker's fluid, and stained with phloxine-methylene blue and phosphotungstic acid hematoxylin. In all autopsies performed under three hours' postmortem, a considerable number of the cases, Zenker's, Helly's and Champy's fluids were used for fixation, as were formalin and Regaud's method. For stains, in addition to phloxine-methylene blue and phosphotungstic acid hematoxylin, the granule stains of Bensley, Lane and Ukai, Mallory's aniline blue and Masson's three-color stains were resorted to. Serial sections were studied in some instances.

In Table 7 are seen the lesions affecting the pancreas as a whole, arranged by decades.

In making the diagnosis "interstitial pancreatitis" only those cases showing clear-cut (though at times focal) increase in interacinar

fibrous tissue with or without fibrous tissue increase in the interlobular septa were accepted and those cases which showed only slight fibrosis were omitted. In a number of instances this fibrosis was accompanied by infiltration to varying degrees with large mononuclears, lymphocytes and rarely eosinophiles. In some instances entire lobules had disappeared with fibrous tissue and scattered islands and ducts remaining. The tendency of this lesion to increase in the older age group is strikingly shown, being entirely absent in the 11 cases under thirty, yet occurring in 36.6 per cent of the 157 cases over thirty years of age. While this frequency is markedly lower than in diabetic individuals in the same age groups, it is nevertheless so great as to preclude considering it a lesion characteristic of diabetes. In non-diabetic individuals it occurs nearly as frequently in association with normal islands as in those whose islands showed pathological change.

TABLE 7.—LESIONS OF THE ENTIRE PANCREAS IN NON-DIABETICS.

Age, yrs.	Cases.	Interstitial pancreatitis.	Lipomatosis.	Acute pancreatitis.	Carcinoma.	Metastatic tumors.	Cysts.	Calculi.	Tuberculosis.
0 to 10 . . .	6	0	0	0	0	0	0	0	0
11 to 20 . . .	2	0	0	0	0	0	0	0	0
21 to 30 . . .	3	0	0	0	0	0	0	0	0
31 to 40 . . .	10	3	0	0	0	0	0	1	0
41 to 50 . . .	34	3	5	2	0	1	0	0	0
51 to 60 . . .	63	23	10	0	1	6	1	0	0
61 to 70 . . .	52	17	8	2	0	6	0	0	1
71 to 80 . . .	28	10	4	1	0	1	1	0	0
81+	2	2	0	0	0	0	0	0	0
Total . . .	200	58	27	5	1	14	2	1	1
Per cent of total .	..	29.0	13.5	2.5	0.5	7.0	1.0	0.5	0.5

It seems unlikely that interacinar fibrosis is a cause of atrophy of the pancreas. Probably far more frequently the fibrosis is a result of atrophy of the parenchymatous tissue from one cause or another with resultant condensation of the stroma than an active factor in the production of pancreatic damage. The analogy to the cirrhotic process in the liver is rather striking.

In many of the cases showing interstitial pancreatitis there is evidence, from the anatomical findings or from the history, of previous gall-bladder disease. In all of these cases of interstitial

pancreatitis fibrous-tissue capsules can be seen about the great majority of the islands, a finding which Otani[2] considers definite evidence of a pathological process.

The criteria used for the diagnosis of lipomatosis are: (1) Separation of the lobules by fat cells, and (2) frequent fat cells occurring among the acini. In this series the presence of lipomatosis in the pancreas was closely related to the amount of body fat. Undoubtedly the proportion of cases showing this would have been much higher were it not for the varying degrees of emaciation, at times extending to almost complete depletion of the stored fat of the body,

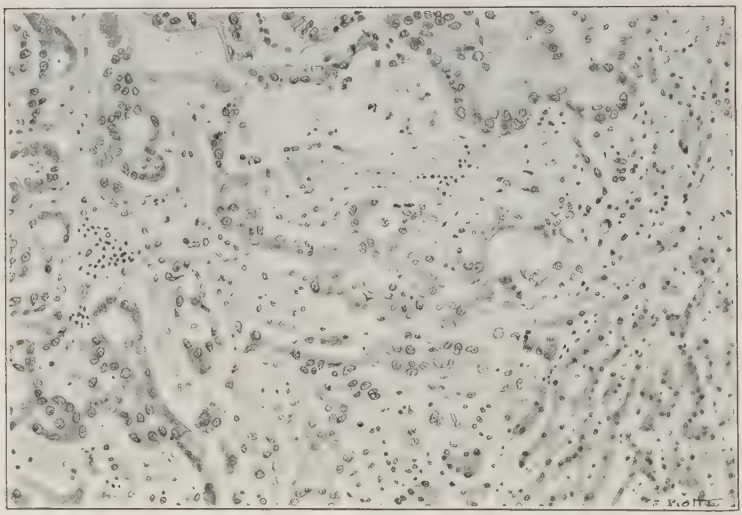

FIG. 33.—Carcinoma of head of pancreas, duct type. Metastasis to liver. Hematoxylin-eosin stain. × 215.

in the cases of malignant disease which were fairly frequent in this series of postmortem examinations. As with interstitial pancreatitis, lipomatosis is associated with normal islands fully as frequently as with diseased islands. It is rather difficult to determine whether stored fat is the only factor in producing this change or whether there is some deposit of fat in response to varying degrees of atrophy of the pancreatic parenchyma.

Primary carcinoma occurred only once, an adenocarcinoma of the head of the pancreas arising from the duct. Many of the islands persisted apparently uninjured in the midst of the tumor tissue and those islands in the uninvaded portion of the pancreas

were also normal. They were not hypertrophic. This incidence of 0.5 per cent contrasts with that of 1 per cent found in my diabetic autopsy series.

Metastatic tumors were frequently encountered as would be expected from the frequency of malignant disease in my post-mortem material. There were 14 cases of metastatic tumor, or 7 per cent. Of these 1 was melanotic sarcoma, 1 myelogenous leukemia, 1 lymphatic leukemia and the remainder carcinoma. In several cases the degree of infiltration was striking, but a sufficient number of islands persisted to maintain normal carbohydrate metabolism.

Tuberculosis of the pancreas was encountered once, as were calculi in the pancreatic ducts. Cysts of the pancreas occurred twice, once apparently the result of a localized acute pancreatitis with subsequent autolysis and once the result of obstruction to the duct of Wirsung by fibrosis of undetermined origin.

Acute pancreatitis, either hemorrhagic or gangrenous, was encountered 5 times. In 4 cases it was the primary cause of death and in 1 it was associated with a staphylococcus pyemia.

The occasional occurrence of lesions in the islands of non-diabetic individuals similar to those found in diabetes is a prerequisite if we consider insular changes the cause rather than the result of diabetes.

Table 8 gives the frequency of lesions in the islands:

TABLE 8.—LESIONS OF THE ISLANDS IN 200 NON-DIABETIC PANCREASES.

Age, yrs.	Cases.	Normal.	Fibrosis.			Hyaline.			Hypertrophy.	Mitoses.	Pyknotic nuclei.	Hydropic degeneration.	Adenoma.	Hemorrhage.
			Slight.	Moderate.	Marked.	Slight.	Moderate.	Marked.						
0 to 10 . .	6	6	0	0	0	0	0	0	0	0	0	0	0	0
11 to 20 . .	2	2	0	0	0	0	0	0	0	0	0	0	0	0
21 to 30 . .	3	3	0	0	0	0	0	0	0	0	0	0	0	0
31 to 40 . .	10	9	0	1	0	0	0	0	0	0	0	0	0	0
41 to 50 . .	34	31	0	0	0	0	1	0	0	0	1	0	1	0
51 to 60 . .	63	54	3	0	0	0	0	1	1	2	1	0	0	1
61 to 70 . .	52	40	5	2	1	0	1	0	1	1	0	1	0	0
71 to 80 . .	28	20	2	1	0	0	1	0	3	0	0	1	0	0
81+ . . .	2	2	0	0	0	0	0	0	0	0	0	0	0	0
Total . .	200	167	10	4	1	0	3	1	5	3	2	2	1	1

This table shows that practically all of the lesions of the islands that are described in diabetic individuals are to be found, although with less frequency, in non-diabetic individuals. Thus, the islands were normal in 83.5 per cent of the cases. Fibrosis of the islands ranging from slight to moderate was present in 7.5 per cent, hyalinization of the islands was present in 2 per cent, hypertrophy of the islands in 2.5 per cent, mitotic figures in the island epithelium in 1.5 per cent, hydropic degeneration (?) in 1 per cent, shrunken cells with pyknotic nuclei in 1 per cent and hemorrhage in the islands and an adenoma of island type, each in 0.5 per cent.

Presumably fibrosis of the islands may be brought about by the same causes that produce the fibrosis of interstitial pancreatitis. This latter lesion appeared in 10 out of 15 pancreases that showed fibrosis of the islands. This is not quite as high a proportion as was noted in our first series.

Hyalinization of the islands has been considered perhaps the most characteristic lesion of diabetes. That the occurrence of this hyalinization was not safe ground for establishing a diagnosis of diabetes pathologically was shown by the case of Ohlmacher,[3] who reported the occurrence of hyaline islands in the pancreas of a non-diabetic, aged seventy-two years, under observation for nine months previous to death. Four-fifths of the islands showed hyaline degeneration, but many of the surviving ones were hypertrophied, which probably accounts for the absence of diabetic symptoms. Saltykow[4] reported hyaline degeneration of some of the islands of Langerhans in the pancreas of a male, aged eighty-eight years, with advanced arteriosclerosis. Cecil,[5] in a careful study of these lesions in non-diabetics, reports 5 cases of his own and 1 of Whipple's. In addition, he states that Milne and Peters[6] mentioned hyaline degeneration of the islands in non-diabetic conditions. There is a rather equivocal case reported by Herxheimer,[7] a patient who had had glycosuria which disappeared on the development of symptoms of cirrhosis of the liver. At the time of death the patient was not diabetic and hyaline islands were found in the pancreas.

I might have paralleled this case of Herxheimer by one of my own (No. 3928), a woman, aged sixty-nine years, who had been known as a mild diabetic, but for some months before death, due to softening of the brain secondary to arteriosclerosis, had shown no glycosuria, probably because her caloric intake was very low. Her pancreas showed hyaline islands. However, in this case a diagnosis of diabetes was made with the help of stains for glycogen, which

demonstrated the typical abnormal glycogen distribution that characterizes diabetic patients. It would have been interesting to know whether Herxheimer's case showed similar changes.

Wright[8] has reported 5 cases, all over fifty years of age, showing varying degrees of hyalinization of the islands associated with slight to marked interacinar fibrosis and showing slight to moderate arteriosclerosis. In this series 3 cases of moderate hyalinization of the islands were encountered and 1 of marked hyalinization, all over forty years of age. The youngest case, one of Cecil's, is thirty-seven years of age. Arrangement and staining properties of the hyaline in non-diabetics is identical with that of the islands of diabetic individuals.

Hypertrophy of the islands was encountered in 5 cases and 4 of these showed fairly marked interstitial pancreatitis. There is some discrepancy in statements as to the normal size of the islands. However, a diameter of 400 micra has been considered the upper normal limit by Cecil,[9] and this has been used as the criterion in the present study.

There is one difference, however, between the hypertrophied islands of the diabetic and the non-diabetic. Frequently the hypertrophied islands of a diabetic individual consist of elongate cells with narrow, centrally located nuclei, whereas the hypertrophied islands in the pancreas of non-diabetic individuals are made up of the usual polyhedral cells with rounded or slightly oval nuclei.

Adenoma of island-cell type is a rare lesion. In 1926 I reported[10] 4 cases and collected 16 others from the literature. In only 1 case, that of Heiberg,[11] was diabetes present. In the present series 1 case was found, occurring in a female, aged forty-four years, dying from epidermoid carcinoma of the cervix uteri.

It is probable that the occurrence of pyknotic nuclei in the island cells is an artefact, at least in non-diabetics, but as this has been considered as a possible diabetic lesion (Gibb and Logan[12]) the occurrence has been recorded in this table.

Similarly, hydropic degeneration, at least so far as it occurs in non-diabetics, is probably due to postmortem change. However, its appearance in the 2 instances in which it occurred in the present series of non-diabetic individuals is similar to that occurring in the islands of diabetic individuals.

Again, hemorrhage in the islands is probably an artefact or at least an agonal change. This lesion was encountered once in the present series.

The pancreatic tissue is fairly insusceptible, so far as actual necrosis is concerned, to injury from toxic causes as compared with such tissues as liver or kidney, and so regenerative changes are rarely seen. This probably accounts for the rarity of diabetes after infections. Mitoses are occasionally encountered in the island cells (3 times in this series), but no more frequently than would be expected in slow replacement of worn-out cells.

The curious epidermoidalization of the ducts, to which attention has been called by Balo and Ballon,[13] Priesel[14] and others was found only once in this series.

It is striking that practically any lesion found in the pancreas of diabetic individuals either involving the island tissue, the acinar tissue or both can be duplicated in the pancreas of non-diabetics. However, the frequency of lesions of the islands is much less in non-diabetic individuals than in diabetics. Therefore, the occurrence of any of the generally accepted insular lesions may be considered as presumptive evidence of diabetes. However, without information of the previous clinical course or without studies of the glycogen distribution in other organs, the diagnosis of diabetes cannot be made. Interstitial pancreatitis occurs too frequently and in too wide a range of disease processes to be considered a characteristic lesion of diabetes. Lipomatosis is probably more nearly related to the amount of stored fat in the body than it is to pathological changes in the pancreas.

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CHAPTER V.

PATHOLOGICAL EVIDENCES OF ABNORMAL CARBOHYDRATE METABOLISM.

Although diabetes mellitus is primarily a disease of carbohydrate metabolism, we know very little from the histological standpoint regarding it. The solubility of the various sugars in the body fluids makes it practically impossible to utilize any of the ordinary histological procedures in study of the problem. The one form of carbohydrate that we can study by histological means, glycogen, is fortunately of great importance, and there are abnormalities of glycogen distribution that characterize diabetes. Some of these changes, such as the glycogenic infiltration of the renal tubular epithelium, were recognized long before their nature was understood. Thus, Armanni[1] described a hyaline vacuolization of the epithelium of Henle's loops unaware that it was due to the presence of glycogen within the epithelial cells.

Since Ehrlich,[2] in 1883, found in 14 cases of diabetes this peculiar infiltration of the epithelium of Henle's loops in the kidneys to be due to the presence of glycogen, this lesion has been regarded as the most definite anatomical finding in active diabetes mellitus. Other less constant abnormal glycogenic deposits associated with the disease were also noted by Ehrlich: The increased glycogen in the heart muscle fibers; glycogenic granules in the leukocytes; and large glycogen-filled vacuoles in the liver cells. Curiously enough, it was not until twenty-three years later that Meixner,[3] soon followed by Best,[4] demonstrated the glycogen-filled vacuoles in the epithelial cells of the liver to be the nuclei.

It is hardly fair to say that glycogenic infiltration of the epithelium of Henle's loops is definite evidence of diabetes mellitus, as glycosuria, from any cause, gives rise to this change. Thus Gierke[5] states it has been found:

1. In diabetes mellitus.
2. After experimental extirpation of the pancreas.
3. After extirpation of the celiac plexus.
4. In phloridzin poisoning.

In the first three instances the blood-sugar level is increased, in the last it is normal, or low. The one point in common is the presence of glucose in the urine.

Since in the great majority of cases glycosuria in the human means diabetes, the presence of glycogen in Henle's loops may for all practical purposes be interpreted as an indication of active diabetes.

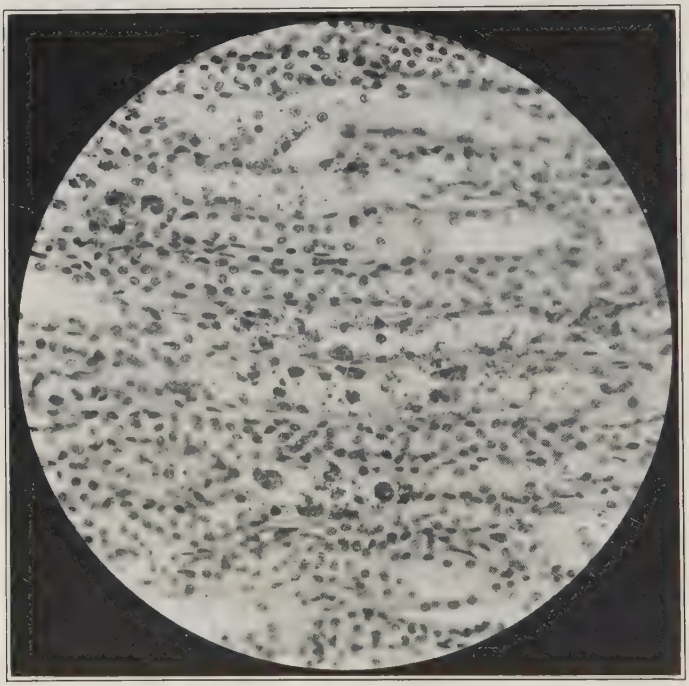

FIG. 34.—Henle's loops of the kidney, showing vacuolization and glycogen granules. M886. Male, aged fifty-four years. Duration of diabetes thirty years. Best's carmine stain. × 170.

It is rather interesting that Ohohashi[6] finds that the distribution of glycogen in the kidney of the diabetic human is exactly the same as that in the normal kidney of the anura. In normal frogs he found traces of glycogen even in the leukocytes. He also mentions that glycogen occurs in the epithelium of the pancreatic ducts in mammalian fetuses. I have found it in this location in several cases of diabetes.

Loescheke[7] gives the following table based on 6 cases of diabetes,

showing the glycogen present elsewhere in the kidneys besides Henle's loops:

TABLE 9.—AMOUNT OF GLYCOGEN IN RENAL EPITHELIUM. (LOESCHEKE.[11])

Case.	Glomeruli.	Convoluted tubules.	Henle's loops.
I	+++	+++	++
II	++	+	+++
III	+	+	++
IV	−	+	++++
V	−	−	+
VI	−	−	+

Rosenberg[8] also mentions a case in which glycogen was present in the glomeruli and the epithelium of the convoluted tubules, as well as in Henle's loops. In certain of the cases summarized in this paper I have found a similar distribution of the glycogen. Sandmeyer[9] gives a quantitative determination of the glycogen present in the kidney of a girl, aged nine years, who had had diabetes for two years, 0.1158 gram per 100 grams of kidney substance. The liver contained 0.6130 gram per 100 grams, or nearly six times as much.

Since pathologists have considered for years that one of the most constant signs of diabetes is the occurrence of glycogen in the epithelium of Henle's loops, it was somewhat disconcerting to me to find in undoubted cases of diabetes mellitus no evidence of abnormal glycogen deposits. In some of these cases glycogen was present in the liver-cell nuclei, but it has long been known that there are many conditions other than diabetes in which there is this intranuclear deposit of glycogen. In fact, approximately one-third of all postmortem examinations show this deposit to a greater or less degree.[10,11]

Methods.—While Best's[12] carmine stain probably is not entirely specific for glycogen, it is none the less the most satisfactory method available for demonstrating this substance. Tissue from surgical specimens or from autopsies is fixed in absolute alcohol and celloidin sections are cut and stained by the Best technique given by Mallory and Wright.[13] As controls, sections placed in saliva for ten minutes were also stained. In certain cases the iodine method of Langhans was also used.

In renal epithelium and liver-cell nuclei the presence of vacuolization as shown in paraffin sections with various stains is a further aid. This vacuolization runs closely parallel with the glycogen content, as shown by Best's stain in tissues fixed under one hour

postmortem, and is much more marked than the carmine stain would indicate in tissues fixed a longer time postmortem.

In most tissues there is a rapid drop in demonstrable glycogen in the first hour, and but little change for some hours thereafter. Yater, Osterberg and Hefke[14] found by microchemical analysis that one-half to three-fourths the glycogen in the rabbit disappears in the first hour and that from then on the rate of decrease is slow.

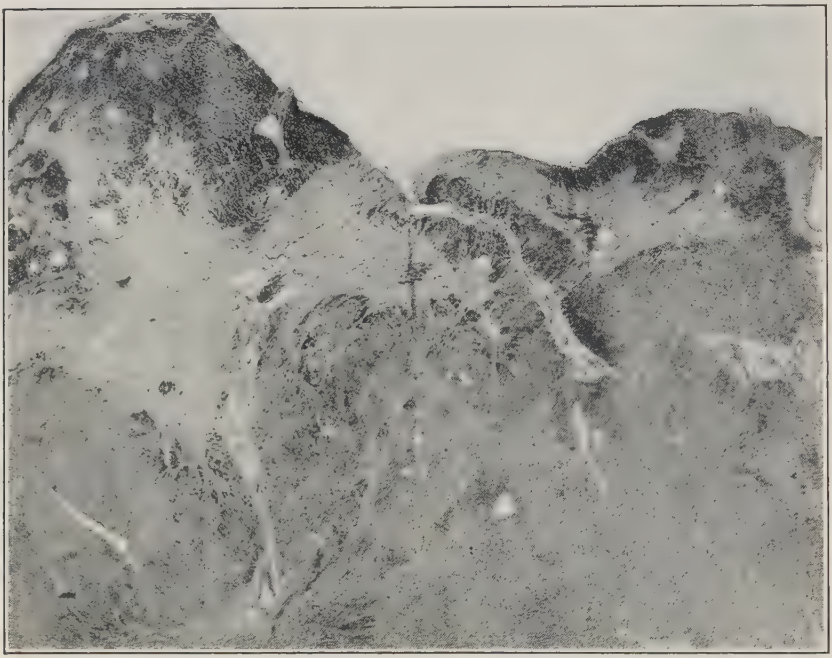

FIG. 35.—Heart. Concentration of glycogen in muscle bundles about foci of fibrosis. Dark portions indicate fibers loaded with glycogen. No. 889. Female, aged sixty-six years. Duration of diabetes fifteen years. Best's carmine stain. × 20.

Results.—Both surgical and postmortem material has been utilized, and the glycogen distribution studied in the various tissues, particularly heart, liver, kidneys, pancreas, voluntary muscle and skin. Both insulin-treated cases of diabetes and cases not treated with insulin are included, as well as a control series of non-diabetics.

Heart: Glycogenic infiltration of the heart muscle is marked in many cases of diabetes. It is particularly striking in those fibers at the margins of infarcts. It can also be found there longer post-

mortem. Whether this means greater storage of glycogen or that the fibers are damaged and so deficient in glycogenolytic ferment is somewhat difficult to decide. On the basis of tissue fixed under thirty minutes' postmortem, an abnormally large storage of glycogen seems the more likely.

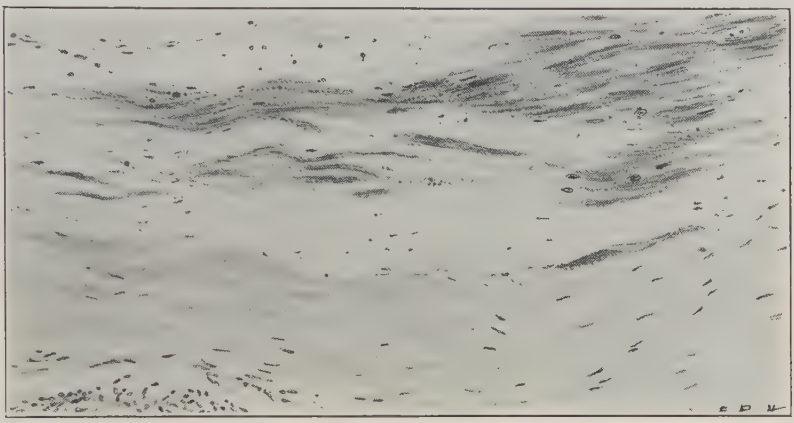

Fig. 36.—Heart. Glycogen in muscle fibers persisting in scar tissue at the margin of a healed infarct. No. 889. Female, aged sixty-six years. Duration of diabetes fifteen years. Best's carmine stain. × 25.

So far as the amount of glycogen in the muscle as a whole is concerned, there is but little difference between the insulin-treated cases of diabetes and the control series. The diabetic cases not treated with insulin show a high proportion of heavy deposits of glycogen.

Table 10.—Glycogen Content of Diabetic Heart Muscle.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin		5	3	6
Insulin		1	..	2
Insulin, infection present		3	8	5
Control (non-diabetics)	2	5	11	5

Liver: Since glycogenic distention of the nuclei of liver cells is found in many other conditions than diabetes, this cannot be regarded as of particular importance. However, in diabetic patients there is a very definite reciprocal relationship between the amount of intranuclear and the amount of intracytoplasmic glycogen. When intranuclear glycogen deposition is marked there is but little or even no glycogen in the liver cells in these cases. Conversely,

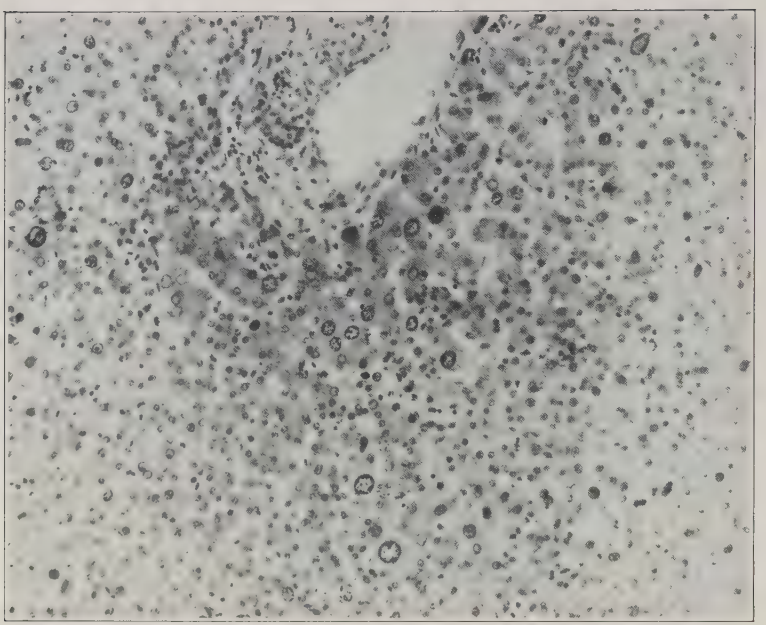

FIG. 37.—Glycogenic infiltration of liver-cell nuclei. Note very slight amount of glycogen in liver cells. Fifty minutes postmortem. DA27-36. Male, aged sixty-six years. Duration of diabetes seven months. × 150.

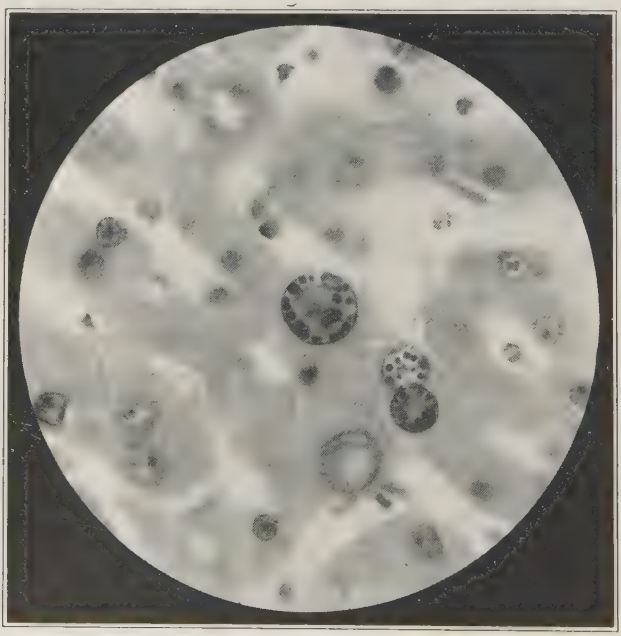

FIG. 38.—Glycogenic infiltration of liver-cell nuclei. Liver cells devoid of glycogen. Best's carmine stain. A22-44. Male, aged seventy-four years. Duration of diabetes eight years. × 500. (Joslin.)

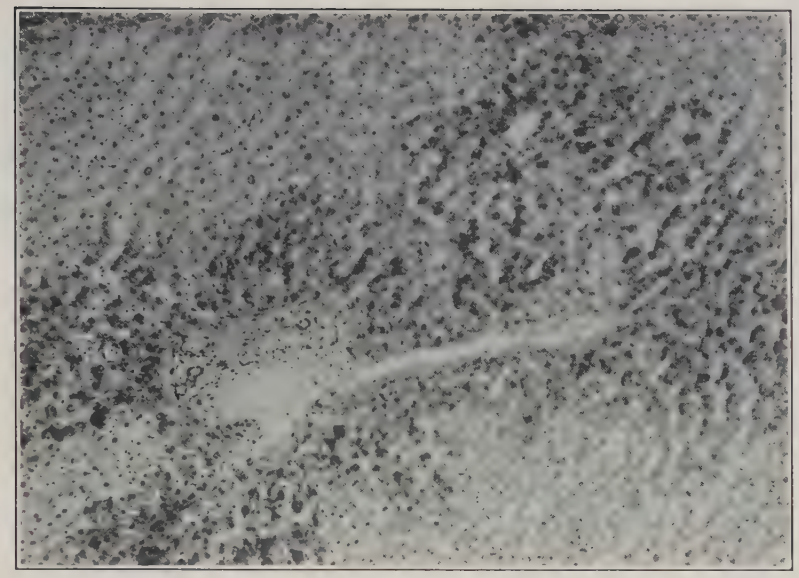

FIG. 39.—Moderate amount of glycogen in cells of periportal zone of liver. No glycogen in liver-cell nuclei. The effect of insulin treatment. DA27-34. Female, aged seventy-three years. Duration of diabetes nine years. Best's carmine stain. × 95.

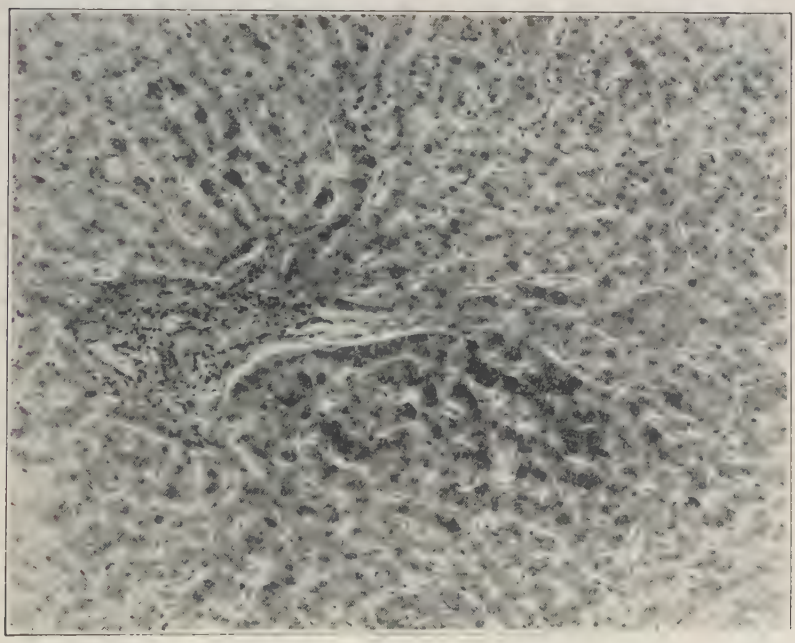

FIG. 40.—Slight amount of glycogen restricted to liver cells of periportal zones. No. 4606. Female, aged sixty-seven years. Duration of diabetes two years. Best's carmine stain. × 95.

when there is much glycogen stored in the cytoplasm, there are few or no nuclei containing it.

TABLE 11.—GLYCOGEN CONTENT OF LIVER-CELL NUCLEI.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	2	11	8	9
Insulin	7	7	1	..
Insulin, infection present	4	9	8	4
Control (non-diabetics)	16	9	3	1

Glycogen is most marked in those cells in the periportal region. Frequently the cells about the central vein contain none, although it is present elsewhere in the lobule in large amounts. There is no antagonism between the deposition of fat and glycogen, both being often present in the same cells in large amounts.

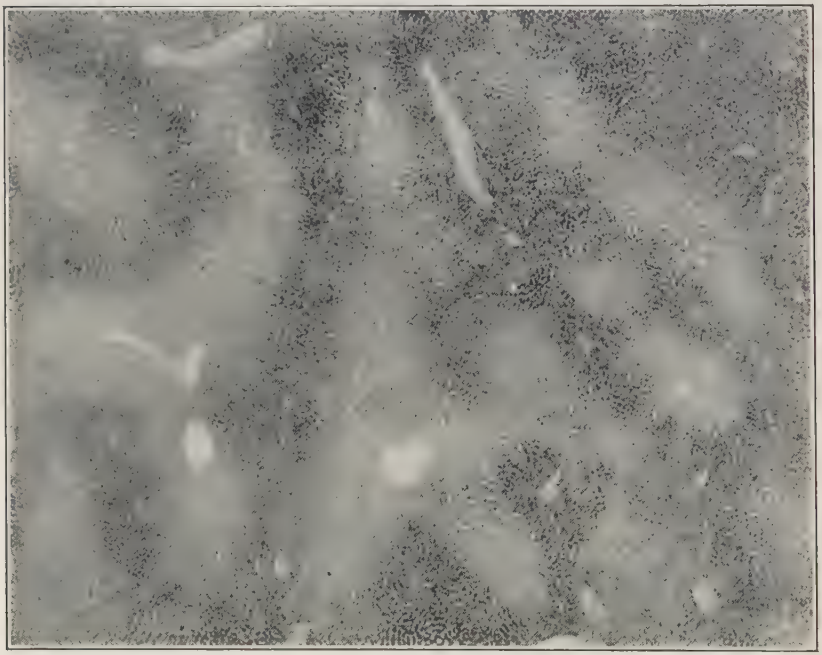

FIG. 41.—Liver showing moderate amount of glycogen, with restriction of deposit to periportal zone. No glycogen in liver-cell nuclei. Effect of insulin treatment. No. 1020. Male, aged fifty years. Duration of diabetes twenty-three years. Best's carmine stain. × 25.

While the physiological basis of this antagonism is well founded, the answer must be sought elsewhere than in the activity of the liver cell.

The histological foundation for the rather prevalent belief in this antagonism is probably the tendency of glycogen to be deposited at the periphery of the lobule first, and fat to be most prominent about the central vein. However, these distributions are probably dependent on the blood supply, the glycogen being synthesized by those cells best supplied with nutriment and oxygen. On the other hand, the fat taken up by the liver cells is metabolized and so rendered invisible in these cells with an adequate blood supply, whereas the cells about the central veins, cells which have to "sit at second table," may be fairly easily loaded with fat which they cannot metabolize and which therefore remains in visible form within the cells.

For some reason the rabbit, in contrast to the human, shows the glycogen deposits to be chiefly in the central portion of the lobule.[15,16] In the dog an even distribution through the lobule is the rule, but in hepatic injury the deposition is most marked about the central veins.[17]

TABLE 12.—GLYCOGEN CONTENT OF LIVER CELLS.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	9	6	6	1
Insulin	..	..	2	3
Insulin, infection present	2	7	4	5
Control (non-diabetics)	1	10	14	4

The above table gives indisputable evidence of the effect of insulin in promoting the deposit of glycogen in the liver, although this effect is somewhat lessened in septic cases. In severe diabetics without insulin even chemical examination may show no or very little glycogen in the liver.[2] The one non-diabetic liver showing no glycogen histologically was a case of healed toxic sclerosis with jaundice. What bearing this may have on the clinical finding that cases of cirrhosis of the liver and diabetes do not do as well under insulin treatment as other cases (see page 179) is uncertain, but it suggests that there may be impairment of carbohydrate storage in cirrhosis. Ravdin[17] has recently summed up the evidence in favor of this view, and concludes that injured liver cells have decreased ability to synthesize and store glycogen. According to Forsgren,[15] in the liver of the normal animal there is an inverse variation of bile and glycogen with one another, in definite relation to meals.

Pancreas: In 8 instances considerable amounts of glycogen and in 12 instances slight amounts were found in the epithelium of the pancreatic ducts, both the smaller ducts with cuboidal epithelium

and the larger ducts with columnar. As has already been mentioned, Ohohashi[6] found this distribution in mammalian fetuses. I have encountered glycogen nowhere else in the pancreas.

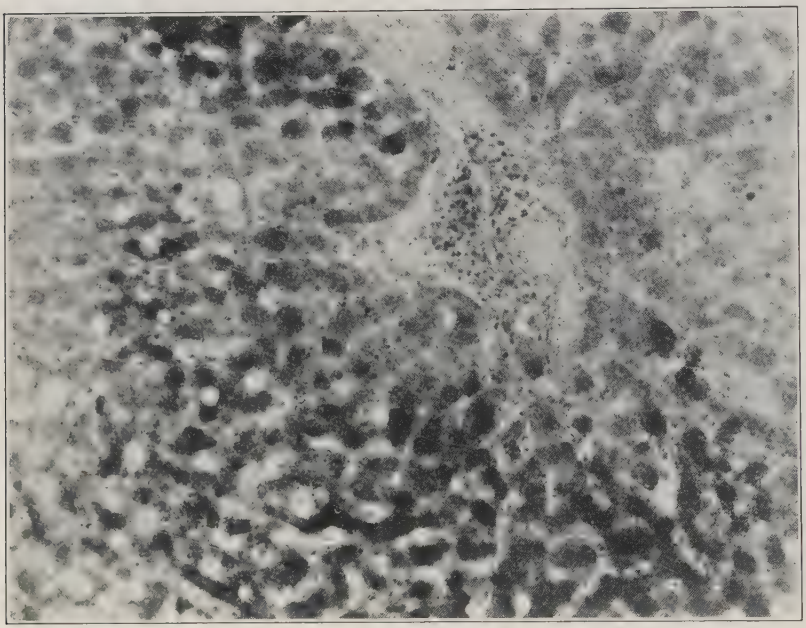

FIG. 42.—Liver showing marked glycogenic infiltration of liver cells. Effect of insulin treatment. Also some fatty infiltration. DA27-71. Female, aged sixty years. Duration of diabetes 1.2 years. Best's carmine stain. × 150.

TABLE 13.—GLYCOGEN CONTENT OF PANCREATIC DUCT CELLS.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	4	6	3	2
Insulin	5	..	..	..
Insulin, infection present	11	6	3	..
Control (non-diabetics)	25	..	..	..

Kidneys: Insulin treatment definitely reduces the amount of glycogen present in the kidneys, as Root and I[18] pointed out. Bornstein[19] has recently confirmed our results. In many cases glycogen is entirely absent. In many others it is considerably reduced over that found in cases of diabetes not treated with insulin. Although Henle's loops are the most typical loci for glycogenic infiltration, the convoluted tubules as well are occasionally involved. This latter localization is sometimes named after Ebstein,[20] who

noted the deposits, but considered them to be necrosis of the cells of the tubules. Glycogenic granules may even be demonstrated

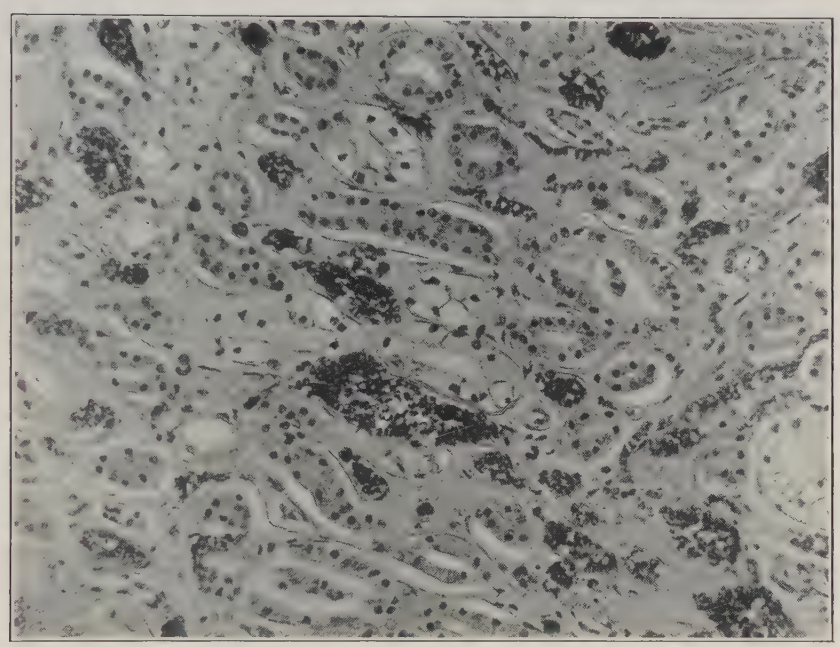

FIG. 43.—Kidney showing marked glycogenic vacuolization of epithelium of convoluted tubules, so-called Ebstein degeneration. No. 5153. Female, aged fifty-six years. Duration of diabetes ten years. Phosphotungstic acid hematoxylin stain. × 225.

within the capsular space, but these probably are artefacts due to postmortem diffusion.

TABLE 14.—GLYCOGEN CONTENT OF KIDNEY.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	3	8	7	25
Insulin	7	3	..	1
Insulin, infection present	1	13	8	8
Control (non-diabetics)	18	1	..	..

Practically every case of active diabetes, either untreated or treated in the pre-insulin days, showed glycogenic infiltration of the epithelium of Henle's loops at autopsy. The presence of this lesion in cases of glycosuria of all types makes one wonder whether or not it represents an attempt of the tubular epithelium to salvage some of the glucose being lost in the urine. Its absence in many

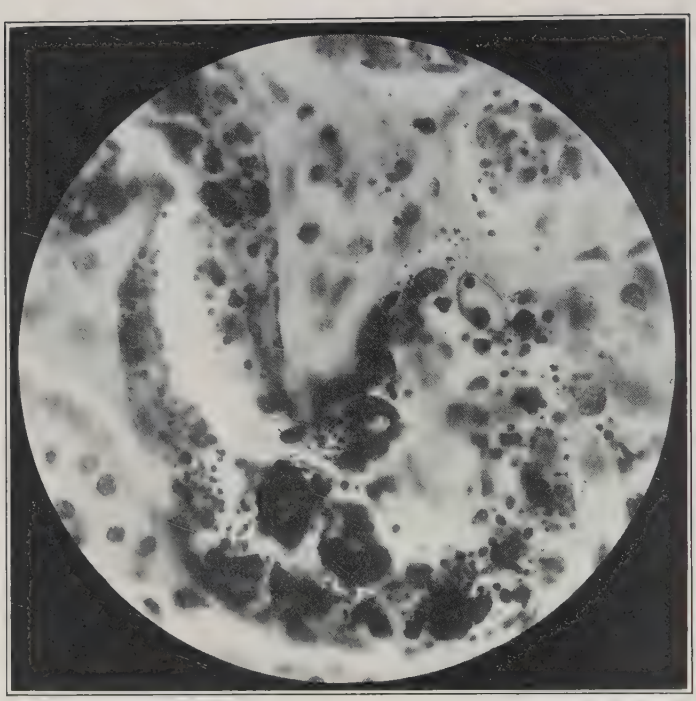

FIG. 44.—Kidney showing marked glycogen deposition in epithelium of Henle's loop. See Fig. 38. A22-44. Male, aged seventy-four years. Duration of diabetes eight years. Best's carmine stain. × 560.

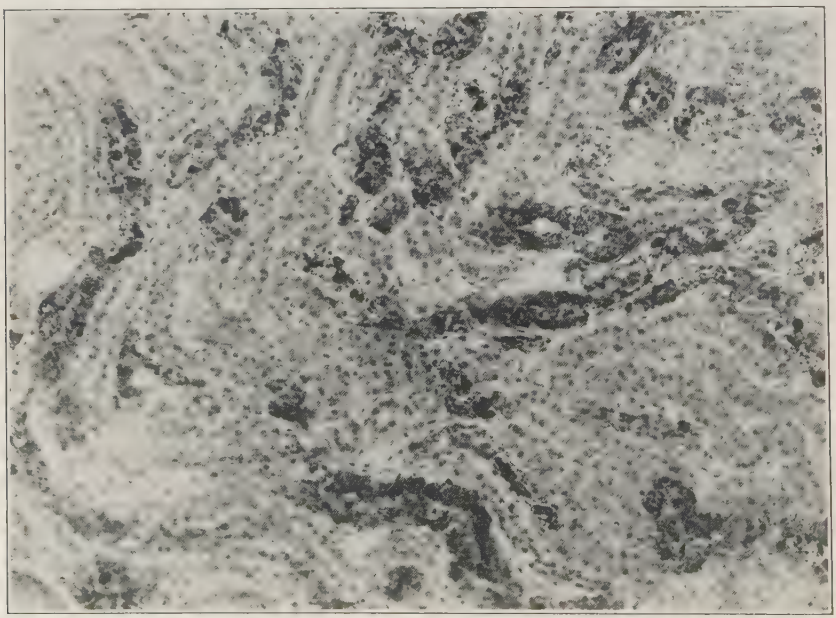

FIG. 45.—Glycogenic infiltration of epithelium of convoluted tubules. Note portion of glomerulus at upper left margin. No. 5153. Female, aged fifty-six years. Duration of diabetes ten years. Best's carmine stain. × 150.

cases treated with insulin shows that it is not an essential lesion of diabetes. This is also indicated by its presence in phloridzin diabetes. Harada[21] believes the glycogen in the epithelium of the kidney pelves, the ureters and the bladder to be the result of cellular activity, being formed from blood and urine sugar.

There is close correspondence between increase in liver-cell glycogen and decrease in renal glycogen, and a similar relationship between liver-cell glycogen and liver-nucleus glycogen. Thus, as normal storage increases under the influence of insulin, pathological storage decreases.[22] This holds true in other organs as well. A diabetic responding satisfactorily to insulin treatment, and dying of some condition other than diabetes or sepsis, such as cerebral hemorrhage, shows very nearly the same distribution of glycogen as does the normal individual.

In a few cases it has been possible to correlate with the glycogen deposits in kidney and liver the blood- and urine-sugar levels obtained within a few hours before death. Typical results are shown in Table 15.

TABLE 15.—RELATION OF GLYCOGEN TO BLOOD AND URINE SUGAR.

Case No.	Insulin.	Blood sugar, per cent.	Urine sugar, per cent.	Liver glycogen.		Kidney glycogen.	
				Cells.	Nuclei.	Henle's loops.	Convoluted tubules.
DA26–55	+	0.44	0.2	+	+	+	−
DA27–12	+	0.48	1.1	++	+	+	−
DA27–33	+	0.57	5.5	+++	+	++	−
DA27–34	+	0.80	3.0	+++	++	+	+
889	+	0.18	0.0	+++	+	−	−
1603	−	0.39	...	+	++	++	+
3709	+	0.28	0.8	+++	+	++	−
5142	−	0.14	0.4	+	+++	++	+
5469	+	...	6.2	++	−	+++	++
5513	+	0.32	2.5	+	++	+++	+

There is a fair degree of correspondence between the urine sugar and the amount of glycogenic infiltration of the kidney, considering that variations in urine sugar must occur rather more rapidly than variations in glycogen content of the renal epithelium.

Voluntary muscle: Many specimens of muscle came from legs amputated for gangrene. They, therefore, may possibly be of dubious value owing to the influence of an impaired circulation,

which would certainly interfere with normal cellular function, and might well influence the function of glycogen storage. However, the muscle was always taken from as near the site of amputation as possible without obtaining traumatized tissue. In this way

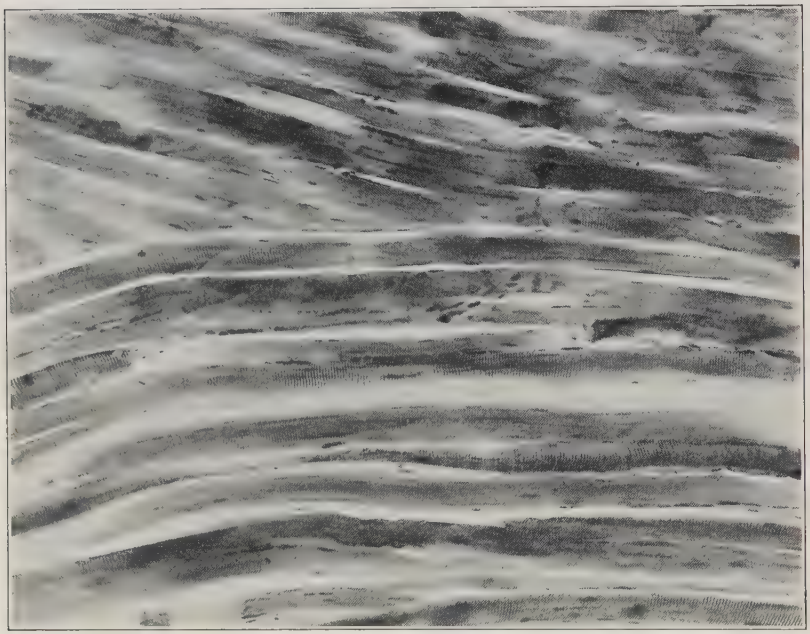

FIG. 46.—Glycogen deposition in striated muscle. This is approximately one-third the amount seen in muscle from normal individuals. No. 4606. Female, aged sixty-seven years. Duration of diabetes two years. Best's carmine stain. × 150.

healthy tissue could be obtained. I am greatly indebted to Dr. L. S. McKittrick for permitting me to make use of fresh surgical material from his cases. In the autopsy material portions of the pectoralis major were utilized.

TABLE 16.—GLYCOGEN CONTENT OF VOLUNTARY MUSCLE.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin	..	1	3	1
Insulin	..	..	1	..
Insulin, infection present	1	13	11	6
Control (non-diabetics)	..	7	12	8

There is a tendency for decrease in muscle glycogen in the cases of diabetes, as would be expected from our knowledge of the disease.

FIG. 1

PLATE II

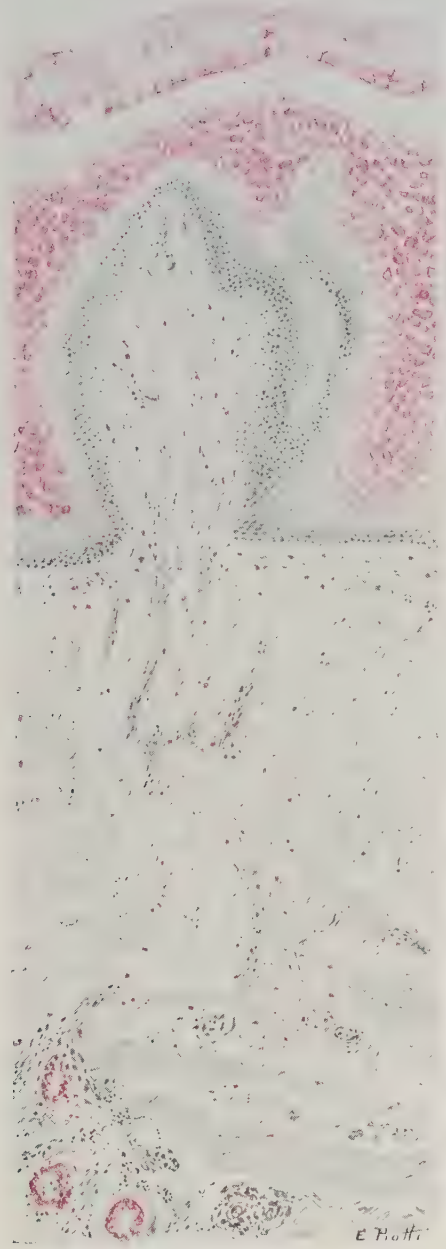

FIG. 2

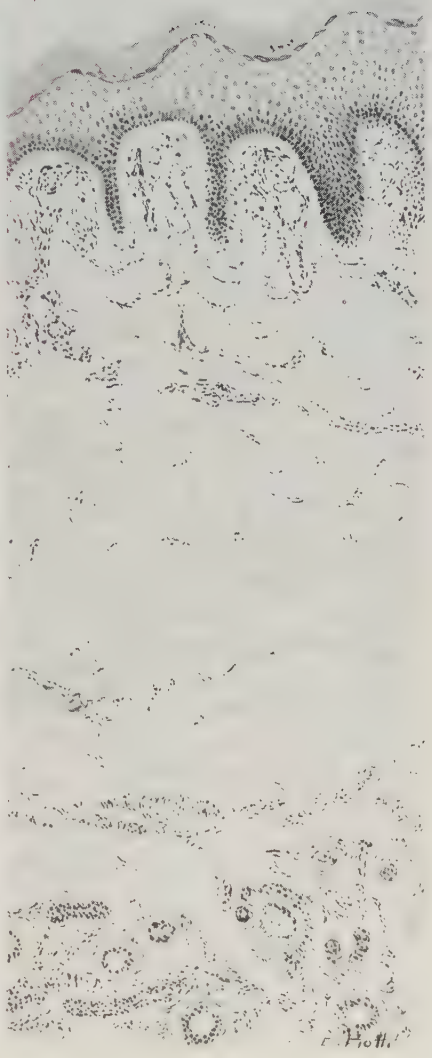

Fig. 1.—Glycogen Deposition in Skin. Note large amount of glycogen in cornified layer and in the keratinizing cells. Also in the epithelium of the coil glands and in scattered mononuclear leukocytes in the corium. No. 4445. Male, aged sixty-two years. Non-diabetic. Leg amputated for arteriosclerotic gangrene. Skin taken from foot. Best's carmine stain. ×90.

Fig. 2.—Skin from Leg. Case of diabetic gangrene. Note the practical absence of glycogen except for a few small deposits in horny layer of epithelium and in leukocytes in corium. No. 2303. Male, aged sixty-three years. A second amputation. Best's carmine stain. ×90.

The muscles contain the great reserve supply of this substance, and only in the mild or fairly adequately treated diabetic can any reserve be built up.

Skin: Unna[23] has recently called attention to the large amount of glycogen in normal skin. Before learning of his work, I had found large amounts of glycogen in the skin of normal individuals and lesser amounts in the skin of diabetics. (See Plate II.) In non-diabetic individuals the epithelium of the stratum corneum, sweat glands, sebaceous glands and hair follicles are heavily loaded. Through the coöperation of Dr. A. M. Greenwood I was able to obtain a number of biopsy specimens of skin, immediately fixed in absolute alcohol, from a variety of skin lesions in non-diabetic patients. Examination of these shows the carbohydrate-storing function of the skin, brought out by Folin and Trimble,[24] includes not only sugar but glycogen. Becker[25] speaks of much glycogen in the duct cells of sweat glands in new-born infants. In a few cases of diabetes the erector pili muscles show heavy deposits when the stores elsewhere in the skin are almost completely depleted. Fichera[26] states that in the depancreatized animal all glycogen disappears except traces in stratified epithelium and in cartilage. Both these tissues are avascular. Dr. H. C. Trimble is very kindly making determinations of glycogen and sugar in normal and diabetic skin and muscle.

TABLE 17.—GLYCOGEN CONTENT OF SKIN.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin		4	..	1
Insulin		1	..	..
Insulin, infection present	5	10	9	4
Control (non-diabetics)		4	18	21

The significance of the variation in glycogen content of the skin is as yet uncertain, but gives a reminder that this organ is by no means inconsiderable as a storehouse for carbohydrate. It is perhaps premature to attempt to correlate variations in cutaneous sugar and glycogen with the well-known susceptibility of the diabetic patient to cutaneous infections.

However, I have seen several instances of skin and muscle infection with Bacillus coli in which there was sufficient production of gas from the carbohydrate present in the tissues to produce crepitation and so simulate gas-bacillus infection. Two of these cases resulted fatally, and bacteriological studies, both postmortem and antemortem, showed only Bacillus coli and staphylococci to be present.

This type of infection I have never seen in non-diabetic patients. Curiously enough the original injury and infection of the skin in both these cases resulted from scratching incident to pruritus, showing this may be a dangerous as well as an annoying symptom.

Brain: In this series so few permissions for postmortem examination of heads have been received that there are insufficient data available. Geipel[27] found glycogen in the cortical cells of 14 out of 19 cases dying of diabetic coma.

Leukocytes: Glycogenic granules were found in the leukocytes of the granulocytic series in 18 cases of diabetes, all of which showed extensive deposits elsewhere typical of diabetes. This finding is less significant as most of the cases were ones with evidence of sepsis.

TABLE 18.—GLYCOGEN CONTENT OF LEUKOCYTES.

Type of treatment.	None.	Slight.	Moderate.	Marked.
No insulin		1	3	6
Insulin		1	..	..
Insulin, infection present		4	3	..
Control (non-diabetics)	2	8	..	..

The advent of insulin treatment is despoiling the pathologist of the one opportunity he had to diagnose with assurance active diabetes. The value of this means of histological diagnosis is well shown by a recent case (No. 3928), where the existence of diabetes was established by the abnormal glycogen distribution. Miss A. P., aged sixty-nine years, was supposed to have had mild diabetes, but the diagnosis was never definitely established. In November, 1928, she developed a left hemiplegia, and gradually grew worse, with mental deterioration. She showed no sugar in her urine, but this was probably due to the low caloric intake, which was little over that which would be allowed a moderately severe diabetic. Death occurred, February 9, 1929, and an autopsy was performed three hours postmortem.

The chief cause of death was multiple foci of necrosis of the cerebrum, secondary to arteriosclerosis. There was chronic pancreatitis, with sclerosis and hyalinization of the islands of Langerhans.

Best's carmine stain showed a slight amount of glycogen in the heart and voluntary muscle, a trace in the liver cells, much in the liver-cell nuclei and a moderate amount in the epithelium of Henle's loops. On these findings a diagnosis of diabetes mellitus was made.

Not only is the glycogen distribution of considerable aid in establishing a diagnosis of diabetes, but it is also of much help in excluding it. As an example, Case No. 7094, a single woman, aged fifty-seven years, entered the hospital under the care of

Dr. E. P. Joslin, December 9, 1929, following a gradual downhill course of two years' duration, with relatively little food intake. She had been advised to enter the hospital several times previously but refused until practically *in extremis*. Physical examination was essentially negative except for weakness and pin-point pupils. Morphine was found in her possession and she admitted having taken considerable amounts for the past two years. December 10, at 11 A.M., Cheyne-Stokes respirations were noticed, her blood-pressure was too low to read, her pupils were still contracted. The nurse stated that during the past three and a half weeks the patient had not taken more than a small fraction of a maintenance diet. December 10, at 11:30 A.M., 1000 cc. of hypertonic glucose solution were given subcutaneously. Subsequently a catheter specimen of urine showed 2 per cent sugar but no acetone or diacetic acid, with blood sugar of 0.67 per cent. No previous urine specimen had been examined, owing to her incontinence of urine and feces. The finding of this urine sugar led to the suspicion of diabetes. Death occurred on December 10, at 9:10 P.M.

However, at autopsy, twelve hours afterward, the pancreas was found to be normal; there was abundant glycogen in the liver and in the muscles; there was no glycogen in the liver-cell nuclei or in the kidneys. In other words, the glycogen distribution was that of a normal individual, not of a diabetic. The probability is that the absorbed glucose could not be metabolized by an individual so near death. The absence of glycogen in the epithelium of the kidney tubules in the presence of a recent glycosuria is probably due to the same fact. The length of time postmortem cannot explain the absence of glycogen here, as there was no vacuolization of the renal epithelium, which persists as presumptive evidence of the presence of glycogen at the time of death until disintegration of the cells. Moreover, normal glycogen deposits were still in evidence. This is the only instance I have encountered of glycosuria without glycogenic infiltration, at least in slight degree, of the kidneys.

The known value of glycogen to the diabetic patient and the striking evidence of the part insulin plays in the deposition of glycogen adduced by these histological studies emphasize the importance of an adequate dosage of insulin. The necessity of preventing infections in diabetic patients is strikingly brought out by the decrease of glycogen storage in insulin-treated cases when sepsis appears. This, of course, parallels the long-recognized observation that tolerance drops during infections.

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CHAPTER VI.

PATHOLOGICAL EVIDENCES OF ABNORMAL FAT METABOLISM.

The frequent occurrence of lipemia and of hypercholesterolemia in diabetes has long been known and very carefully studied.[1,2] Naturally less attention has been attracted by the rather rare abnormal deposition of lipoid material in various organs, or rather in the reticulo-endothelial cells.

I. THE SPLEEN AND RETICULO-ENDOTHELIAL SYSTEM.

This deposition, when present, is more marked in the spleen than in other organs. The rarity of the condition in its full-blown state is striking. I have encountered it in only 6 out of 300 diabetic autopsies. Through the kindness of Dr. I. B. Rabinowitch, I have been able to examine the tissues in a case[3] of his (Montreal General Hospital, A28-3), which showed extraordinarily rapid disappearance of fat from the circulating blood (from 11.6 to 6.8 per cent in less than twelve hours). Death was due to coma. The spleen was not typical of the cases of lipoid histiocytosis, but occasional reticulo-endothelial cells showed marked vacuolization, and the Kupffer cells of the liver were strikingly vacuolated.

Much of the following discussion of lipoid deposits in the spleen has been taken from an article by Root and myself:[4]

While in the average spleen removed at autopsy there is little evidence, either gross or microscopic, of lipoid content, Poscharisky[5] demonstrated fat to be present in spleens removed from cases of many different diseases and to be more abundant in those spleens containing amyloid and hyaline masses. This fat is present in small droplets and gives the characteristic staining reactions for neutral fat. He further states that in children the fat is chiefly within the "epithelioid" cells of lymph nodules of the spleen, while in adults it is found in the pulp, trabeculæ, capsule and vessel walls.

Kusunoki[6] added further proof of the frequent though inconspicuous occurrence of lipoid in the spleen, and showed that most was contained in cells of the reticulum. The lipoid gave the following staining reactions: Red with Sudan III, black with osmic

acid and blue or blue-violet with Nile blue sulphate. Kusunoki also found the number and prominence of the lipoid-containing cells in the spleen to run parallel with the lipoid content of the blood.

Aside from this fairly common finding of rare lipoid-containing cells in the spleen, there are a few cases of diabetes with lipemia recorded in which very marked hyperplasia of these cells occurs, and the lipoid present does not, as a rule, give the staining reactions usually encountered.

The first instance of this striking change in the spleen was mentioned by Coats.[7] The patient, suffering from diabetes with lipemia, had died in coma. Large lipoid-containing cells made up most of the splenic tissue. Other cases have since been reported. The findings in 8 of these are summarized and compared in Table 19 with those in 3 of our cases.

TABLE 19.—COMPARISON OF STAINING REACTIONS OF VARIOUS FATS FOUND IN THE SPLEEN.* (WARREN AND ROOT.[4])

Case No.	Type of lipoid.	Sudan III.	Scarlet-red.	Nile blue sulphate.	Osmic acid.	Smith-Dietrich.	Aniso-tropic crystals.
I. 1305	1	Red	Red	Blue	Black	+	Few.
	2	Yellow	Faint	Faint rose	Faint	+	Few.
II. 1794	..	Yellow	Faint	Faint rose	Faint brown	+	Few.
III. 05-172	..	Orange	Red				
IV. Schultze[8]	..	Faint	Faint	Faint rose	−	+	−
V. Lutz[9]	1	Faint	...	Faint rose	−	...	...
	2	Red	...	Blue	−	...	Few.
	3	Red	...	Bright rose	Black		
VI. Lutz	1	Red	...	Rose	Black	...	...
	2	Yellow-red	...	Violet	Black	...	...
VII. Marchand[10]	..	Yellow	...	...	Faint	...	...
VIII. Williams and Dresbach[11]	..	+	...	+	...	...	+
IX. Smith[12]	1	Red	Red	Blue	Black	+	−
	2	Faint	Faint	Faint rose	Faint	Gray reticulation	−
X. Fahr and Stamm[13]	..	−	...	−	...	...	+
XI. Oppenheimer and Fishberg[14]	..	−	...	...	...	−	...

* In some of the cases there are various types of lipoid present.

The third case of this rare lesion was brought to our attention by Dr. F. B. Mallory. This cannot be studied as carefully as we should wish since the autopsy was performed twenty-four years ago and the material other than the slides has been lost. Case IV was encountered in a series of juvenile diabetics studied by Page and myself.[15] The sixth case was the oldest in the group, a man, aged fifty-two years. The first 2 cases were under careful observation for five and eight years respectively, and an abundance of material was available for study.

Case Histories.—Case I.—No. 1305. White male. Onset of diabetes at ten years and six months of age. Maximum body weight (clothed), 75 pounds (12 per cent above normal). The illness lasted five and a half years. The last few weeks he received small amounts of insulin, but died in coma.

Table 20.—Blood Changes in Case I, No. 1305.

Date.	Blood sugar, gm. per 100 cc.	Blood fat,* per cent.	
May 22, 1917	0.09	..	
Nov. 17, 1919	0.21	..	
Dec. 1, 1919	..	0.51	
June 3, 1921	0.25	1.00	
Jan. 3, 1922	0.24	1.68	
Feb. 13, 1922	0.22	1.72	
Aug. 9, 1922	0.20	0.92	Given small
Aug. 28, 1922	0.21	1.61	amounts of
Sept. 3, 1922	..	1.54	insulin.
Oct. 20, 1922	..	2.56 2.30 1.80	During coma.

* Analyses by Bloor's[16] total fat method. (Normal, 0.75 per cent.)

In Table 20 are given a few selected blood-sugar and blood-fat analyses which serve to show the general character of the blood changes.

Autopsy Report.—Age, sixteen years. Autopsy one hour post-mortem. Limited to upper abdominal incision. The body is that of a fairly well-developed and well-nourished white boy. No edema. No jaundice.

Heart.—Normal size. No gross evidence of fibrosis. Valves negative. The coronary arteries are negative.

Lungs.—Soft, crepitant except at bases, which are somewhat soggy. On section, both bases are moist and reddish, with fluid in bronchi.

Spleen.—Not remarkable.

Pancreas.—Small.

Gastro-intestinal Tract.—Negative.

Liver.—Not remarkable. The bile ducts are patent. The gall bladder is negative.

Kidneys.—Negative.

Aorta.—Scattered atheromatous plaques.

Anatomical Diagnoses.—Hypostatic congestion of lungs, early arteriosclerosis.

Microscopic Findings. - Heart.—Moderate amount of subepicardial fat. There is a slight increase of fibrous tissue.

Lung.—Congested. A few polymorphonuclear leukocytes and red blood cells, together with endothelial leukocytes containing pigment, in alveoli. A few polymorphonuclear leukocytes and lymphocytes in submucosa of bronchi. Moderate amount of carbon pigment beneath pleuræ and about larger vessels and bronchi.

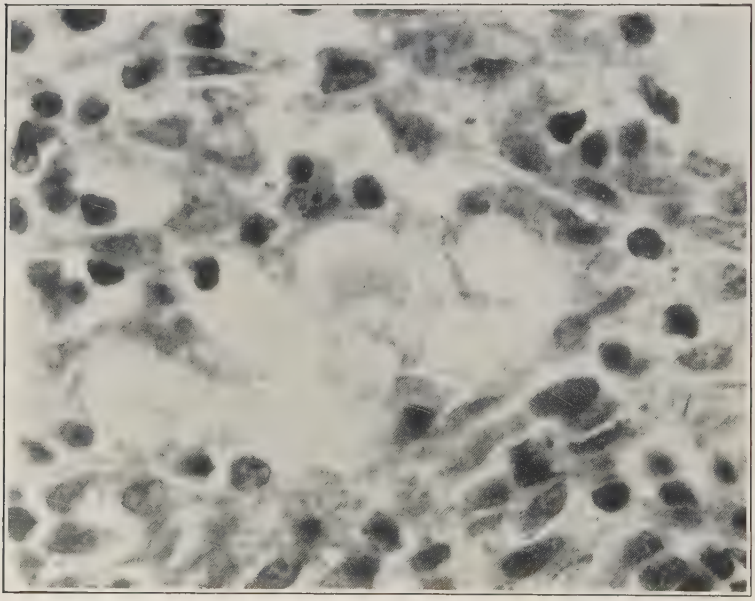

FIG. 47.—Lipoid histiocytosis of spleen. Case M978. Male, aged sixteen years. Duration of diabetes five and a half years. Death in coma with marked lipemia. Eosin-methylene blue stain. × 500.

Spleen. Large vacuolated cells resembling endothelial leukocytes are present in the lymph nodules and in the splenic pulp. These cells are most prominent in the outer portions of the lymph nodules. (Fig. 47.) Some lymph nodules have reddish hyaline material in their centers, and a few contain scattered phagocytic

endothelial leukocytes. Moderate degree of hyaline thickening of walls of arterioles.

With fat stains on formalin-fixed tissue preserved for three years there appear to be two types of fat present (Table 19, Case I). The first type, occurring in the larger globules found among the cells in the outer part of the lymph nodules as a rule, stains deep red with Sudan III and scarlet-red, blue with Nile blue sulphate and brownish-black with osmic acid. The second type occurs in smaller droplets in endothelial leukocytes both in the splenic pulp and to a less extent in the lymph nodules, as well as in the hyaline substance noted above and occasionally free in the neighborhood of small blood vessels. These droplets stain yellow-red with Sudan III, a faint red with scarlet-red, very faint rose with Nile blue sulphate and pale gray with osmic acid. Both types of fat stain with the Smith-Dietrich method. With the polariscope, when the slide is warmed, a few anisotropic crystals are detected, which disappear with further heating but reappear on cooling. These findings are summarized in Table 19 (Case I).

Pancreas.—Congested. Slight increase in connective tissue of islands. Moderate increase in interlobular connective tissue.

Liver.—Fine vacuoles suggesting fat occur in the endothelium of the sinusoids. These stain red with Sudan III and scarlet-red, and brownish-black with osmic acid. The liver cells are vacuolated, especially about the central veins, and give similar staining reactions.

Kidneys.—Not remarkable.

Case II.—No. 1794. White female. Onset of diabetes at twenty-five years of age. Body weight at onset, 130 pounds. Duration of disease, eight years. On June 6, 1920, blood sugar was 0.25 gram per 100 cc. and blood fat was 1.1 per cent. On May 21, 1921, blood sugar was 0.20 gram per 100 cc. and blood fat was 0.8 per cent. In June, 1922, she weighed, when clothed, 71 pounds. Under insulin treatment she gained weight and strength, and in June, 1925, shortly before her death, weighed 135 pounds. After breaking diet she became suddenly ill with severe pain in the left chest and arm. She had five Stokes-Adams seizures, and died after a few hours from cardiac failure.

Autopsy Report.—Age, thirty-three years. Weight, 130 pounds. Autopsy one hour postmortem. The body is that of a well developed and nourished white female. No edema. No jaundice. Abdominal fat layer $1\frac{1}{4}$ inches thick.

Peritoneal Cavity.—Surfaces smooth and shining. No free fluid.

Pleural Cavities.—Negative.

Pericardial Cavity.—Negative.

Heart.—Weight, 315 grams. Epicardium negative. Considerable subepicardial fat. Apex of left ventricle yellowish-gray, opaque and separated from normal myocardium by thin red zone. On section, lower two-thirds of interventricular septum is similar in appearance. A large thrombus is adherent to endocardium. This entire region stains intensely red with scarlet-red. In the endocardium just below the aortic ring are yellowish raised plaques which also surround the coronary orifices. The right coronary artery shows numerous atheromata; both branches of the left are tortuous and sclerosed. The first portion of the left barely admits a horsehair.

Spleen.—Somewhat grayish. Only a small amount of pulp can be scraped away.

Pancreas.—Weight, 60 grams. Negative in gross.

Liver.—Weight, 1835 grams. Yellowish-red. Bile ducts are patent. Gall bladder is distended with bile.

Kidneys.—Weight, 350 grams. Negative in gross.

Adrenals.—Negative.

Bladder.—Negative.

Genitalia.—Negative.

Aorta.—Numerous atheromatous plaques.

Anatomical Diagnoses.—Infarct of heart, coronary sclerosis and arteriosclerosis.

Microscopic Findings.—Heart.—Moderate ingrowth of fat. Numerous hemorrhages into myocardium with polymorphonuclear leukocytes between the fibers. In several foci muscle fibers have lost their striations and normal staining reaction, and have granular or hydropic cytoplasm. Numerous vessels are plugged with fibrin, the meshes of which contain red blood cells and polymorphonuclear leukocytes. In one place there is marked fibrous thickening of the endocardium with hemorrhages beneath. Closely attached to the endocardium are masses of fibrin with red blood cells and polymorphonuclear leukocytes enmeshed. The coronary arteries show marked thickening of the intima, due to collections of vacuolated and pigmented endothelial leukocytes. When stained for fat, the material in these cells is shown to be similar to that in the spleen.

Lungs. Edema. Carbon pigment is present beneath pleura and about larger vessels.

Spleen. Congested. Numerous plasma cells occur throughout. A large number of endothelial leukocytes filled with fat droplets are distributed throughout the pulp and are particularly abundant in the germinal centers. Some of the cells contain numerous droplets, while others are greatly distended by one large droplet. The large ones are apparently due to the coalescence of droplets originally contained in endothelial leukocytes but set free by degeneration of the cells. The germinal centers are few, and most of them contain masses of hyaline material. One contains a network of fibrin.

The results obtained with fat stains (on tissue fixed in formalin for five months) are summarized in Table 19 (Case II). In this spleen only one type of fat appears to be present. It stains yellow with Sudan III, faint yellow-red with scarlet-red, very pale rose with Nile blue sulphate and very pale brown with osmic acid. Osmic acid appears to stain only the periphery of the globules, but they stain well with the Smith-Dietrich method. The polariscope reveals a few anisotropic crystals when the section is warmed, which disappear on further heating and reappear on cooling.

Pancreas. There is slight increase in the interlobular connective tissue. The islands appear to be much fewer than normal. Islands can be found showing degrees of fibrosis varying from apparently normal to practically complete disappearance of island cells.

Liver.—The periportal areas contain numerous polymorphonuclear leukocytes, lymphocytes and plasma cells. Rarely a few of the liver cells at the periphery of the lobules are necrotic and surrounded by endothelial and polymorphonuclear leukocytes. Bile stasis is apparent in some portions. Endothelial leukocytes in the sinusoids are phagocytizing pigment, and some contain fine droplets. When stained for fat these droplets are yellow with Sudan III and pale violet with Nile blue sulphate.

Kidneys.—The glomeruli are markedly congested. The tubules are edematous. In Henle's loops the epithelial cells have lost all substance except for the nucleus and are greatly distended.

Aorta.—There is very marked fibrous thickening of the intima in which are many endothelial leukocytes containing fat droplets. A few lymphocytes are also present. The vessels of the media are surrounded by an increased amount of fibrous tissue, with moderate infiltration by endothelial leukocytes. The droplets in the endothelial leukocytes when tested for fat are stained yellow with Sudan III and blue-black by the Smith-Dietrich method. With polarized light the droplets are found to be anisotropic.

Case III.—No. 05-172. Emaciated white male, aged twenty-one years, was admitted to the hospital in deep coma and with a marked odor of acetone on the breath. No history could be obtained and death occurred in thirty hours. The urine showed a large amount of sugar and of diacetic acid, as well as a slight trace of albumin.

Autopsy Report.—The significant findings in the autopsy may be summarized as follows:

Heart.—When the blood was placed in a cylinder a layer of creamy, bluish-white fluid occupied the upper three-fifths of the column. The myocardium shows small scattered foci which are slightly darker than the surrounding tissue, translucent and slightly depressed.

Spleen.—Weight, 320 grams. On section, dark red, firm, with markings distinct. A very small amount of pulp comes away on scraping.

Aorta.—There are a number of opaque yellow raised plaques in the intima of the ascending portion of the arch. These are fewer in the remainder of the aorta, and they tend to cluster about the mouths of the intercostal arteries.

Microscopic Findings.—Heart.—Sections of formalin-fixed material stained with scarlet-red show fat droplets in the muscle fibers.

Spleen.—There is moderate congestion. The meshes of the reticulum are filled with large foamy cells. When sections of formalin-fixed material are stained with scarlet-red these cells contain orange masses. The vessels contain much finely-divided fat. In some of the nodules the endothelial cells show evidence of proliferation. There is an increased number of eosinophiles.

Liver.—There is considerable congestion. The nuclei are vacuolated, giving the typical appearance of glycogenic infiltration. The endothelial cells lining the sinusoids are somewhat enlarged and finely vacuolated. Sections stained with scarlet-red show fine fat droplets evenly distributed through the liver cells and the endothelial cells.

Kidneys.—The epithelium of the tubules is markedly vacuolated. In sections of formalin-fixed tissue stained with scarlet-red these vacuoles are seen to be filled with fat except in the region of Henle's loops. The character of the vacuolization here suggests glycogenic infiltration. There is also finely-divided fat in the glomeruli and in the blood vessels.

Lymph Nodes.—The sinuses are dilated and filled with vacuolated endothelial cells, some of which are in mitosis. In some of the lymph nodules there is an increased number of endothelial cells at the center. The endothelial cells contain finely-divided fat.

Case IV.—P H 9949. Female, colored, aged twelve years. Duration of diabetes, four years. Past history essentially negative. January 7, 1925, admitted and placed on diet of carbohydrate, 120; protein, 60; fat, 115; with insulin, 32 units per day, which kept her sugar-free. June 8, 1925, admitted in coma. Blood sugar, 0.65 per cent. Rapidly recovered under coma therapy. May 26, 1927, admitted in coma. Blood sugar, 0.28 per cent; plasma CO_2, 17.6 volumes per cent. Recovered rapidly under coma therapy; kept sugar-free with insulin, 45 units per day. October 31, 1927, coma four days after sore throat. Blood sugar, 0.43 per cent; plasma CO_2, 14.0 volumes per cent. Death thirteen hours after admission. Autopsy findings: An undernourished and underdeveloped negro girl. Focus of confluent bronchopneumonia in right upper lobe with pleuritis. Heart, weight, 120 grams. There are numerous small atheromatous plaques along the bases of the aortic cusps, otherwise negative. The aorta shows numerous raised, bright-yellow atheromatous plaques about the mouths of the coronary arteries. About the intercostal arteries and in the abdominal portion are numerous small, raised, yellow atheromatous plaques. Liver shows fatty infiltration. Pancreas is negative in gross and microscopically, except for early postmortem change. The spleen on microscopic examination shows a number of cells containing droplets of fat and the liver shows extensive fatty infiltration and droplets of fat in the Kupffer cells throughout. Microscopic examination of the aorta shows extensive lipoid infiltration in the intima with fraying of the internal elastic lamina.

Case V.—No. 1020. Male, aged fifty years. Diabetes for years. Two years before death right leg amputated for gangrene. Shortly before death large carbuncle developed on neck and blood culture was positive for Staphylococcus aureus.

Autopsy Report.—Extensive carbuncle of neck. Septic thrombosis of right lateral sinus with meningitis, multiple abscesses of lungs, heart and kidney, lipoid histiocytosis of spleen.

Spleen.—Weight, 200 grams. Unusually pale. Considerable amount of pulp can be scraped away.

Microscopic examination shows the reticulo-endothelial cells of nodules and of sinusoids to be markedly vacuolated. Frozen sections stained with Sudan IV show these vacuoles to be due to the presence of fat.

Moderate arteriosclerosis of aorta with marked involvement of iliac arteries.

Case VI.—(Dr. R. H. Jaffé.) Cook County Hospital. No. 1927-3. White male, aged fifty-two years. Duration of diabetes unknown. Entered the hospital with bronchopneumonia and died soon after.

Autopsy Report.—Bronchopneumonia, gangrene of right lower lobe of lung, healed infarcts of heart, marked coronary sclerosis, chronic pancreatitis, arteriosclerosis, arteriosclerotic atrophy of brain, infarcts of spleen, lipoid histiocytosis.

Spleen. Enlarged and pale. Numerous recent infarcts. Microscopic examination shows considerable amounts of intracellular lipoid in the centers of the lymph nodules and small amounts in the endothelium of the blood vessels and the sinusoids. *Liver* shows a moderate amount of fatty infiltration in the liver cells and considerable amount of lipoid giving the staining reactions of neutral fat in Kupffer cells. There is a moderate degree of atheromatosis of the aorta and extreme atheromatosis of the vessels of the circle of Willis with partial atrophy of the brain.

It will be noted in these cases that, while the spleen was most striking, the reticulo-endothelial cells elsewhere were involved. So far as can be judged from the staining reactions, the lipoid is present in various forms, and sometimes even varies in the same case, though cholesterol esters or related substances predominate. Thus, in Case I the larger droplets are presumably soaps or fatty acids, among which, according to the reaction with osmic acid, are unsaturated fatty acids. The smaller droplets contain cholesterol esters.

One of the puzzling features of this condition is the variation in chemical constitution of the lipoids taken up by the cells of the reticulo-endothelial system, and the difference between these lipoids and those of the blood. Of course the staining reactions are not entirely reliable criteria, but in several of the cases of this condition there is marked difference in the reactions of the lipoid material in the circulating blood and that present in the reticulo-endothelial

system. The selective absorption of cholesterol compounds and phosphatides seems not impossible.

In this involvement of the spleen the occurrence of the lipoid-containing cells in the pulp and the lymph nodules, in addition to lining the sinusoids, serves as differential diagnosis from Gaucher's disease, in which the lipoid-containing cells are entirely within the sinusoids. In the lipoid histiocytosis of diabetes the spleen never attains the large size of Gaucher's disease. There is, however, marked resemblance in appearance between the lipoid-containing reticulo-endothelial cells in both these conditions.

Anitschkow[17] produced a somewhat similar picture in the spleen of animals by experimental feeding with cholesterol. Aschoff[18] classes together these two conditions in the xanthelasmic diseases.

The lipoid stored in Gaucher's disease is chiefly kerasin.[19,20]

The essential splenohepatomegaly of Pick-Niemann must be distinguished from the lipoid cell hyperplasia encountered in diabetes. In this former condition the lipoid-laden cells are present in the pulp.[21,22] Here the lipoids are chiefly lecithin and cholesterol. The material present in the diabetic lipoid histiocytosis is somewhat different, cholesterol, fatty acids and neutral fats predominating, with a small amount of phosphatides, if we may trust the rather uncertain results of staining reactions. An excellent review of the condition in diabetes is given by Smith.[12]

As I have previously pointed out, atheromata of the aorta are very frequently associated with this condition in diabetes regardless of age. Thus, in the case of Oppenheimer and Fishberg[14] atheromatous patches were found in the intima of the aorta and in the endocardium of a girl, aged six years. Atheromata were found in the aorta of our Case I, only sixteen years of age; and our Case II, thirty-three years of age, died of infarct of the heart resulting from marked atheromatosis and sclerosis of the coronary arteries, with involvement of the aorta as well. Case III, aged twenty-one years, showed numerous atheromatous patches in the intima of the aorta, as did Case IV, aged twelve years. In Case V the presence of arteriosclerosis was not remarkable, as the age at death was fifty years.

II. THE SKIN.

The association of xanthomas of the skin and diabetes has long been known, "xanthoma diabeticorum" being a familiar phrase to every medical student. The careful studies of Wile[23] have shown

that cases of xanthoma need not be associated with increased blood cholesterol, and he separates the xanthoma palpebrarum or xanthelasma from the true xanthoma.

In my diabetic series true xanthomas are extremely rare in spite of the fact that hypercholesterolemia is fairly frequent.[24] Wile[23] has shown that, although crystals of cholesterol may frequently be present in xanthomas, nevertheless their prominence is more apparent than real. The amount of cholesterol was less than 20 per cent of the total lipoids (the normal for cutaneous epithelium) in 3 cases that he examined and only made up 2 per cent of the total tumor by weight. One of Wile's cases was a diabetic. When the patient was placed on a practically fat-free, low-caloric diet the multiple xanthomas which she had decreased markedly in size. Later the patient was placed on a relatively high-fat diet on which she became sugar-free and the tumors showed an even more rapid disappearance. On resumption of normal diet the xanthomas reappeared.

Most important of all, the cholesterol in these lesions may not be present in greater amount than in normal human body fat, and the largest portion of the fat content of cutaneous xanthomas consists of lipoids other than cholesterol, suggesting that the xanthomas may be in some instances merely an abnormal site of deposition of normal fat.

However, occasional cases, a section from one of which is shown in Fig. 48, show greater relative amounts of cholesterol. In this case cholesterol made up 45 per cent of the lipoid present, though only 1.6 per cent of the total mass. Curiously enough, the tumors in this patient, stable as cholesterol deposits seem to be in the body, disappeared as rapidly under dietary and insulin treatment as do the ordinary xanthomas.

Bloor[25] notes that the xanthoma and xanthelasma cells are typically macrophages filled with anisotropic lipoids (cholesterol esters).

The highest blood cholesterol value associated with xanthoma found in this laboratory is 781 mg. per 100 cc. In practically all cases of xanthoma reduction of the fat in the diet has reduced the blood lipoid and has resulted in the disappearance of the xanthoma.

The presence of true xanthoma is a strong hint that the diet needs revision from the standpoint of lowering the lipoid intake.

Still another factor to be considered is that the diet of the average diabetic patient is rich in lipochromes and local cutaneous lipoid deposits may very well be emphasized by deposition in them of

lipochromes with the establishment of the common xanthoma palpebrarum or xanthoma.

Carotinemia is, of course, a not infrequent finding in diabetes. The necessity of using in the diabetic diet large amounts of pigmented vegetables and eggs forces much lipochrome into the body. This usually is adequately taken care of, but may be present in the blood in sufficient concentration to produce visible pigmentation. Rabinowitch[26] views carotinemia as a grave prognostic sign.

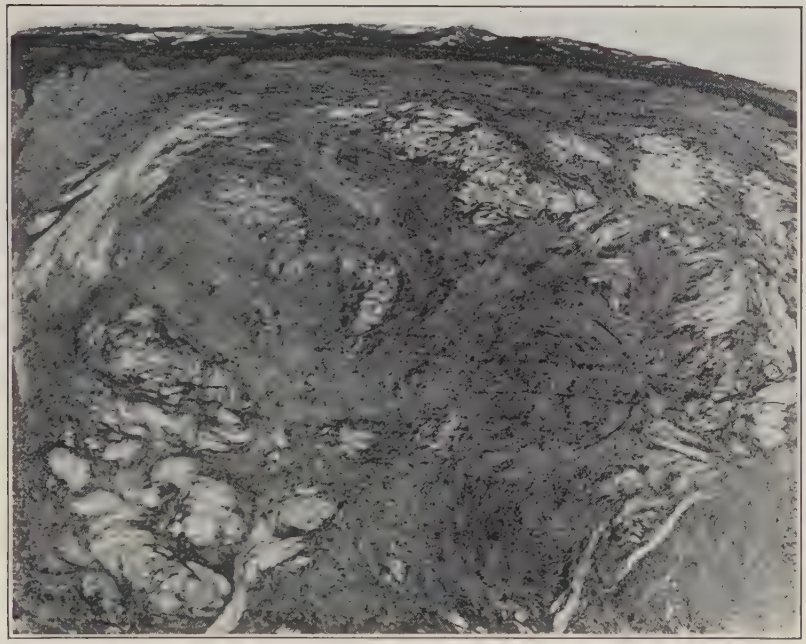

FIG. 48.—Section of xanthoma of skin showing numerous masses of cholesterol crystals imbedded in dense connective tissue. Male, aged forty-eight years. Duration of diabetes eight years. Similar lesions to this shown in section cleared up under insulin treatment. Hematoxylin-eosin stain. × 20.

Broek and Yater[27] do not agree with him on this point, as they encountered among 100 diabetics 86 cases of xanthemia. However, xanthosis was present in only 9, and 3 of these were in a state of acidosis, 1 recovered from coma a week before, and 3 were severe diabetics.

Connor[28] found the normal range of carotinemia to be from 0.0 to 0.07 mg., and he found in 18 diabetic patients of Joslin's selected

at random values ranging from 0.05 to 0.16 mg. Miss Hunt in this laboratory has found in 19 determinations on diabetic patients who were clinically suspected of carotinemia the values range from 0.09 to 0.86 mg.

III. THE GALL BLADDER.

Inasmuch as the bile is the chief route for elimination of cholesterol from the body, and many gall stones are of the cholesterol type, abnormalities of the gall bladder might be expected as a result of the disturbed lipoid metabolism in diabetes. Table 21 shows the incidence of gall stones and cholecystitis in a group of autopsied diabetics over thirty years of age and in 400 non-diabetic autopsies in the same age group.

TABLE 21.—FREQUENCY OF GALL-BLADDER LESIONS IN AUTOPSIED CASES OVER THIRTY YEARS OF AGE.

	Diabetic.	Non-diabetic.
Number of cases	245	400
Cholelithiasis	62	54
Cholecystitis without stone	19	5
Previous operative removal of gall bladder	4	13
Carcinoma	1	1

Table 22, from Ophüls,[29] shows the incidence of gall stones by age groups in 3000 autopsies, of which only 34 were performed upon diabetics.

TABLE 22.—RELATIVE INCIDENCE OF GALL STONES AT DIFFERENT AGES. (OPHÜLS.)

Age, yrs.	Number of cases.	Percentage of total.
20 to 30	3	1.2
30 to 40	19	4.2
40 to 50	33	5.9
50 to 60	53	9.4
60 to 70	62	13.3
70+	36	19.1

The available statistics as to the occurrence of gall stones vary greatly, from 3 per cent in White's[30] series of 11,031 autopsies based on Guy's Hospital material, to 21 per cent in Mentzer's[31] series of 600 autopsies at the Mayo Clinic. Kaufmann[32] at Basle found 10.9 per cent of 16,025 autopsies to show gall stones.

Wilder[33] reported 16 cases of cholelithiasis and 4 of severe cholecystitis in 58 autopsies on diabetic patients, performed at the Mayo Clinic, or 28 per cent with cholelithiasis and 34.5 per cent with gall-bladder disease. This compares closely with my findings (22 per

cent of 300 autopsies showing cholelithiasis and 28.3 per cent showing either cholelithiasis or cholecystitis).

This increased prevalence of cholelithiasis and cholecystitis in diabetes is of obvious importance from two angles: The gall-bladder disease in itself, and the marked depression of sugar tolerance exerted by any inflammatory process in the diabetic organism.

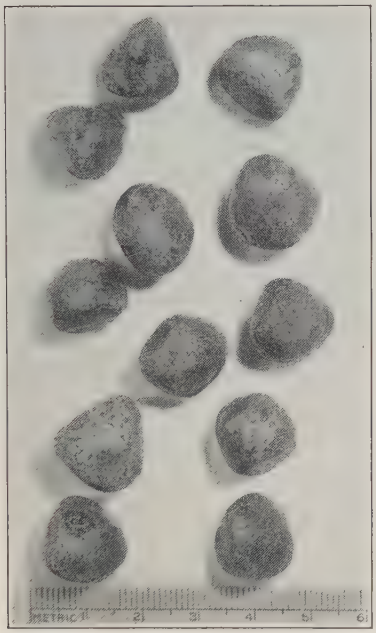

FIG. 49.—Gall stones, largely cholesterol, from Case DA27-95. Female, aged sixty years. Duration of diabetes five years. These stones were found at autopsy. There had been no definite symptomatology pointing toward them.

In view of the stress laid on gall-bladder disease as a possible cause of pancreatic injury, and hence diabetes, it is of interest to consider whether diabetes or gall-bladder disease appeared first in these cases. In most instances the onset of diabetes antedated the appearance of symptoms referable to the gall-bladder disease. This, of course, is of little value as evidence, as the stones were silent in many cases. Moreover, Joslin's cases, with more detailed clinical data, showed the gall-bladder disease to develop first. Relatively few of the cases examined postmortem show sufficient pancreatic change of inflammatory type to admit pancreatitis due

to gall-bladder disease as a cause of the diabetes, although practically all show some pancreatic fibrosis of slight to moderate degree.

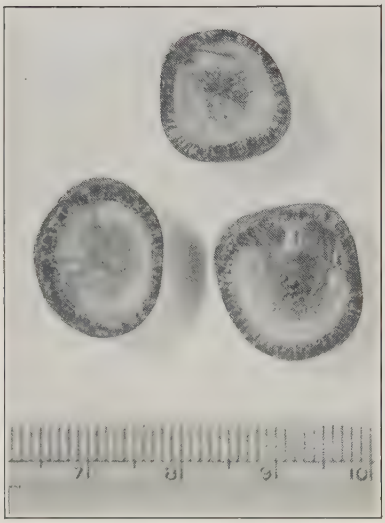

Fig. 50.—Cross-section of several of the stones shown in Fig. 49. Slightly enlarged.

In a few instances, as Case A15-17 (Peter Bent Brigham Hospital), the gall stones in all probability predisposed to repeated attacks of acute pancreatitis of mild type, with eventually sufficient injury to the islands of Langerhans to permit diabetes to develop. This case occurred in a male, aged fifty-seven years. For five years attacks of pain in the right upper quadrant recurred at intervals, with occasional periods of jaundice. One month before death from bronchopneumonia diabetes of moderate severity developed. At autopsy three large stones were found in a thick-walled gall bladder. The pancreas showed patches of fat necrosis and fibrosis. The islands were hypertrophied.

However, cases of this type are rare. In Table 23 the occurrence of gall stones in my series is compared in various periods of duration of the diabetic process.

Table 23.—Relation of Gall Stones to Duration of Diabetes.

Duration of diabetes, yrs.	Per cent with gall stones.
0 to 5	14.9
5 to 10	27.5
10 to 15	47.4
15+	30.4
?	20.0

Of course the known mildness of "gall-stone diabetes" may account for the strikingly increased occurrence of gall stones in the cases of longer duration.

The association of cholelithiasis with arteriosclerosis is also marked. Of course this might well be explained by the tendency of both to occur in the upper age groups, but the strikingly high incidence of both these lesions in diabetes suggests a common origin, probably in the disordered fat metabolism.

Therefore, the stone may best be considered a result of disturbed lipoid metabolism, dependent on the diabetes.

Joslin[34] cites a striking case, No. 310, who developed diabetes at the age of seventeen years. When only twenty-one years of age gall stones were definitely diagnosed. Death occurred in coma when thirty-eight years of age.

The bulk of stones found are of the cholesterol type, though occasionally the pigment-calcium stones are encountered. A few examples of analyses from a series of diabetic and non-diabetic gall stones performed by Dr. J. DuFrates in this laboratory are given below and illustrate the marked variation in chemical constitution that may occur among stones from diabetics. However, the frequent occurrence of cholesterol-rich stones in the diabetic series and the statistical evidence suggest a connection between diabetes, hypercholesterolemia and gall stones.

TABLE 24.—ANALYSES OF GALL STONES (DRY WEIGHT).

Case No.	Diabetes.	Number of stones.	Cholesterol, per cent.	Calcium, per cent.
793	−	1	96.4	..
4319	+	..	0.15	34.6
Avery	+	..	93.2	1.3
Clough	+	..	91.5	0.92

Wilder[33] felt that the unusually high incidence of gall stones in diabetics previously reported by Root and myself[35] could not be substantiated by the results in his series, although his figures were comparable to ours, as he considered the difference in prevalence between his diabetic and control series slight. However, it must be remembered that the control series which he used for comparison was based on material from the Mayo Clinic which would naturally be weighted with cases of gall-stone disease.

There is no one type of stone that occurs to the exclusion of others as the figures well show, although if any could be picked out as typical, I should consider it the large ovoid stone made up of a mass of radiating cholesterol crystals with or without a small amount of calcium and pigment.

To sum up, diabetics are known to have a disturbed fat metabolism, gall stones are more common in diabetic than in non-diabetic individuals, and other disorders of lipoid metabolism frequently develop in diabetic individuals.

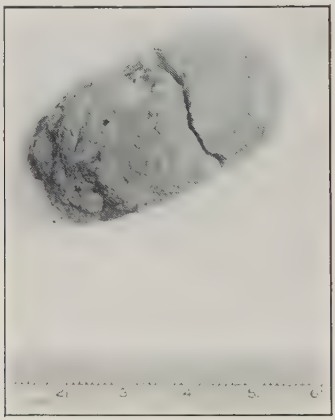

FIG. 51.—Large single cholesterol stone with small amount of calcium at one end found in non-diabetic patient. Female, aged fifty-one years.

FIG. 52.—Calcium and pigment stones from female, aged sixty years. Duration of diabetes 10.7 years. This is one of the few cases of diabetes showing the calcium or pigment stone rather than the cholesterol type of stone.

Since the abnormal lipoid metabolism which originally produced the stones persists after operation, and since the presence of stone in the gall bladder may be a definite factor in lowering carbohydrate tolerance in diabetes, cholecystectomy should be performed on all diabetic patients with evidence of gall-bladder disease.

IV. THE LIVER.

One of the oldest references to the pathology of diabetes is to the marked fatty infiltration of the liver that is sometimes present. Mead[36] called attention to this in 1748. Adelsberg and Porges[37] consider an enlarged and fatty liver as a regular finding in diabetes. In my series marked fatty infiltration in the liver has been encountered from time to time, but is in no sense a regular finding. Raab[38] has shown that marked fat deposition can be caused in the liver by administration of pituitrin, which may be used in very minute amounts if injected intracerebrally in animals.

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CHAPTER VII.

THE PATHOLOGY OF ACIDOSIS AND COMA.

Acidosis and coma are closely allied with abnormal fat metabolism, although more particularly with the soluble end-products of incomplete combustion of fats than with the lipoids themselves. Instead of dealing with localized and readily demonstrable deposits of lipoid substances in the reticulo-endothelial cells, in the skin and in the gall bladder, we have to deal with widely distributed abnormal end-products of fat metabolism which, unlike the fats themselves, are soluble in the body fluids and hence diffusible, thereby exerting a considerable effect on the various cells of the body but are not in themselves demonstrable. This diffusibility, of course, profoundly affects the pathological picture, as the changes produced are general rather than local, and only the end-results of the action of these substances on the parenchymal cells can be demonstrated by histological means.

The occurrence of the so-called acetone bodies is not restricted to diabetic patients, but may appear in normal individuals during starvation, and are particularly apt to appear in those individuals who are fat.

However, it is in diabetes that the largest amounts are produced. Joslin[1] mentions his Case No. 4 as excreting 437 grams of β-oxybutyric acid during three days of coma. This corresponded in this patient to 1 gram of hydrochloric acid per kilo per day. The chief burden of eliminating these substances from the body is thrown on the kidneys (although to some degree the lungs participate in the excretion of acetone).

The rapidity of the development of acidosis and its sequel, coma, depends not only on the rate and amount of production of acid bodies but also on the amount excreted and the rate of excretion, which are closely linked with the condition of the kidneys, as well as the amount of acid bodies taken up by the bases of the blood, with displacement of the combined carbon dioxide.

As diabetics have a striking tendency to develop arteriosclerosis,

which often leads to arteriosclerotic nephritis, the kidneys of those in the older age groups are frequently already impaired when needed to deal with the maintenance of acid-base equilibrium. Thus acidosis may be somewhat more likely to develop than in normal individuals, even given an equal production of acetone bodies.

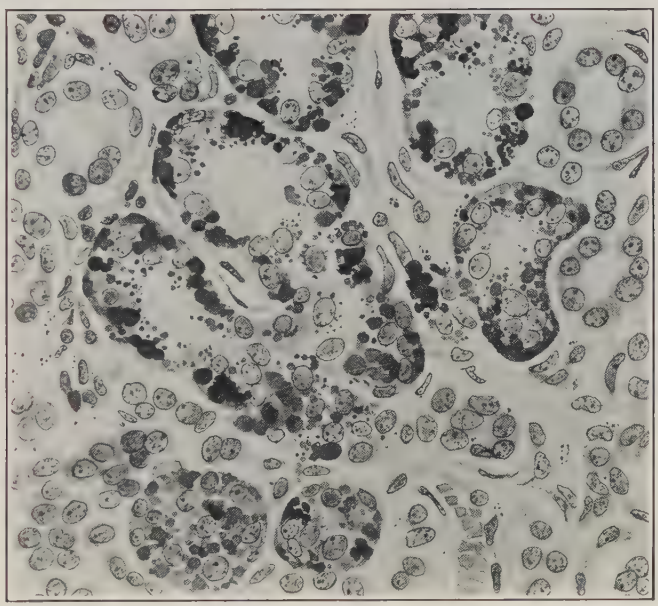

FIG. 53.—Fat in tubular epithelium in tubular nephritis in a case of diabetes with sepsis. Diabetes of unknown duration. Sudan IV stain. × 500.

Now the changes produced by acidosis of the acetone body type are, so far as can be seen, but little different from those seen in the acidosis so readily produced by intoxication of animals with various mineral acids, such as those produced by the prolonged administration of hydrochloric acid. A tubular nephritis due to toxic injury of the epithelial cells is a very frequent finding, and still more impairs renal function, thus furthering the development of a vicious circle. This tubular nephritis is the cause of the showers of casts in the urine, so frequently associated with acidosis.

One of the most important factors associated with the development of diabetic acidosis is the depletion of stored glycogen in the

body. The more glycogen reserve there is to call upon the less fat has to be metabolized, and the more complete is the combustion of such fat as is utilized. Here the glycogen-forming effect of insulin, noted in Chapter V, is of tremendous value.

The culmination of acidosis is coma. While the pathological physiology of diabetic coma is very familiar and is well understood, at least from the symptomatic standpoint, the pathological changes in coma are conspicuous by their absence. Even in pre-insulin days when diabetic coma developed in uncomplicated cases of diabetes there were no characteristic pathological changes that would enable one at postmortem or on looking at a section of tissue to say, "This material came from a case of diabetic coma." Today the same holds true.

However, we do know that depletion of the stored glycogen predisposes to acidosis and to coma. In cases of coma one sees at their best the various forms of pathological distribution of glycogen, together with the absence of normal deposits, which were discussed in Chapter V. In fact, some authors[2] have endeavored to explain the development of coma on the basis of glycogenic infiltration and vacuolization of the cortical cells. Although I have not been able to perform satisfactory glycogen stains on cerebral tissue from many cases of diabetic coma, in the few cases that I have examined I cannot substantiate this theory.

Unfortunately, coma does not always develop at a certain stage of acidosis, and there may be considerable discrepancy, coma appearing in certain cases with acid-base ratio not far from normal, and in others only with extreme acidosis.

There is a marked difference in the associated pathology of coma cases of the pre-insulin era and those that are insulin-treated. Moreover, this difference is of tremendous importance to both patient and physician. In the days before insulin coma represented the triumph of the uncomplicated diabetic process over the organism, but now coma developing in insulin-treated cases means that the diabetic process is receiving extraneous aid in its struggle and this aid is generally sepsis. Practically the only exception to this is in those insulin-treated cases who omit insulin, and as a result of metabolism of their body fat rapidly develop acidosis.

If coma develops in a well-treated diabetic it practically always means infection. If a patient with diabetic coma dies in spite of insulin therapy, it is usually difficult for the pathologist to say

whether the patient died from the pathological physiological changes that characterize coma, complicated by sepsis, or died of a septic process complicated by the terminal development of diabetic coma. Sepsis is the worst enemy of insulin.

This antagonism between septic processes and insulin, autogenous or injected, is all too well known clinically. A diabetic patient, treated or untreated, loses tolerance with even minor infections. This is as true today as in the pre-insulin days. When attacked by infection an insulin-treated diabetic requires more insulin during the course of the intercurrent disease and promptly drops back to his former requirements when the infection is past. The tables in Chapter V bring out vividly the fact that the one anatomically visible feature of carbohydrate metabolism, glycogen storage, tends to approach that of the normal individual in insulin-treated cases, but that in cases with sepsis the picture tends toward that of the untreated diabetic in spite of insulin. Whether this is a direct antagonism it is impossible to say. Much more likely, of course, is the general effect of the bacterial products in interfering with the normal response of the tissues.

From the standpoint of prognosis we are justified in saying that a case of diabetic coma free from infection should recover with adequate treatment regardless of age or the severity of the diabetes. On the other hand, a case of diabetic coma with infection present is in an extremely dangerous position.

Joslin's Case No. 6770, aged seventy-two years, was admitted to the hospital in deep coma. She had had a partial thyroidectomy some years before, also removal of one kidney and cholecystectomy for gall stones. On admission at 8 A.M. her rectal temperature was 93.4° F.; her blood-pressure was too low to read; urine sugar, 2.8 per cent; blood sugar, 1.0 per cent; blood CO_2, 6 volumes per cent. With coma treatment, including 440 units of insulin, she had practically recovered by 6 A.M. the next day, with blood sugar of 0.13 per cent; blood CO_2, 34 per cent; blood-pressure, 120/50. This is a striking example of what can be accomplished in coma cases not complicated by infection.

Let us consider the typical pathological findings in a case of acidosis progressing to death from coma, in a non-insulin-treated diabetic. The only changes which we find are those characteristic of prolonged acidosis practically nothing but a tubular nephritis, sometimes with evidence of toxic injury to the liver cells.

The kidneys are responsible for severe functional disturbances, and some of the cases at autopsy show varying degrees of acute tubular nephritis. Anuria or oliguria is not infrequent.[3]

Rarely renal insufficiency may be so marked as to prevent the excretion of the acetone bodies in coma, so that ketonuria may not appear.[4] Nitrogen retention may be very marked, and showers of casts and albumin be present in the urine.

However, the changes in the epithelium of the renal tubules in cases dying of coma are not comparable with the acute tubular nephritis of toxic origin. The necrosis is less marked; the absence of polymorphonuclear leukocytic exudate is striking.

Startlingly prompt is the return to normal function after recovery from coma, suggesting the pathological changes are still reversible.

The liver cells are practically devoid of glycogen, their nuclei distended with it. The epithelium of the kidney tubules shows large amounts, the heart muscle is increased, while the striated muscle and skin are depleted.

The pancreas may show almost any type of lesion in the islands or in the acinar tissue, or it may show none. Fulminating cases of diabetes rapidly progressing to coma and death frequently show hydropic degeneration of the islands.

One fairly frequent postmortem finding is the occurrence of blood, fresh or partly digested, in the stomach and intestinal tract. Usually no bleeding-point can be found and presumably capillary hemorrhages rather than gross bleeding-points are their source. At times the stomach in particular is tremendously dilated, causing marked distress. This distention may be a cause rather than an effect of hemorrhage through mechanical stretching of capillaries, although a direct chemical effect on the capillary endothelium must be considered in those cases with marked acidosis.

A few of these coma cases were accompanied, as would be expected, by disturbed metabolism of the higher lipoid substances. Of the 6 cases of abnormal lipoid distribution described in Chapter VI, 3 died in coma.

Striking evidence that the anatomical changes in uncomplicated coma are reversible, and hence short of actual cell destruction is given by the clinical course. Given a case of coma pure and simple, insulin treatment brings prompt recovery, far more rapid than would have been possible if any marked injury were present.

While in the pre-insulin era coma was not infrequently precipi-

tated by some minor infection, nevertheless it more often occurred as a result of the diabetic process itself.

The picture changes when we analyze the insulin-treated cases of coma. Here the pathology accompanying coma is of varied type, almost as varied as in the cases of diabetes which do not die of coma, because the effect of the infection is not so much an acceleration of the diabetic process itself as it is direct injury to the organism. In other words, the associated pathology found with some insulin-treated cases of coma is not only the precipitating cause of the coma but frequently would be fatal in itself.

The important thing to keep in mind in this rôle of infection is that infection not only is antagonistic to insulin through reducing glycogen storage and thereby rendering coma more likely to develop, but also infection exerts a direct damaging effect upon the organism, which is rendered far more susceptible to acidosis thereby. The reserve factor of safety is reduced and consequently coma is much more apt to develop. This is strongly shown now, as the bulk of fatal coma cases occur in elderly individuals, those in whom disease processes have produced damage, whereas the children, relatively free from associated disease, are easily protected from coma by insulin.

The development of insulin treatment has strikingly altered the picture in so far as deaths from coma are concerned.

Uncomplicated coma was the cause of death in 53 cases studied in this series, whereas 38 cases died from coma accompanied by or induced by septic processes. Cerebral hemorrhage and pulmonary embolism were the immediate cause of death in 1 case each. In the uncomplicated coma cases practically all the deaths occurred in cases who died before the discovery of insulin or in cases that were treated only after entering the hospital, usually late in the development of coma.

The most frequent infection to precipitate fatal coma is pneumonia, ordinarily bronchopneumonia rather than lobar. Pneumonia alone or accompanied by pericarditis led to 16 of the coma deaths, or 22.4 per cent of the total. The next most important precipitating factor was gangrene, leading to 8 or 10.9 per cent of the coma deaths.

Streptococcus or staphylococcus septicemia was responsible for 7, or 9.6 per cent. Thirteen other cases of septicemia died without the development of coma. In these insulin kept the diabetes under control.

Coma with or without infection may be accompanied by a high white cell count, which greatly complicates the picture from the clinical standpoint. A white cell count as high as 97,000 with frequent myelocytes has been reported[5] in coma, without any evidence of infection, and the blood picture returned to normal and remained so after recovery from coma.

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CHAPTER VIII.

ARTERIOSCLEROSIS AND GANGRENE.

ARTERIOSCLEROSIS.

Whether the increased prevalence of arteriosclerosis in diabetes is due to the disease itself or to methods of treatment of the disease, the importance of the problem is such that it cannot be disregarded. I have yet to see at autopsy a diabetic or to read the autopsy protocol of a diabetic, whose disease has lasted five years or more, free from arteriosclerosis, regardless of age. However, I hasten to add with real pleasure that I have never performed a postmortem examination on a young person who has had diabetes five years or more with insulin treatment throughout the course of the disease. Such cases rarely die as a result of their diabetes.

Of course, many of my cases fall in the older age groups and, therefore, would be expected to have arteriosclerosis in any event. However, the cases in the younger age groups frequently show this lesion, as has been pointed out in Chapter VI in considering the pathological evidences of abnormal fat metabolism. If we accept Aschoff's[1] modification of Virchow's imbibition theory of arteriosclerosis, it is obvious that blood plasma laden with lipoid will predispose to the development of arteriosclerosis, and the lesion may be correlated with abnormal metabolism.

Table 25 from Joslin[2] compares the proportion of arteriosclerotic deaths among 604 fatal cases of diabetes that occurred during the Banting Era with the relative incidence of arteriosclerotic deaths among the total deaths in Massachusetts in 1925. This table illustrates the premature development of arteriosclerosis among diabetics.

However, it is not enough for us to be content with mortality statistics. We must know what is going on in the living diabetic patient as well, that we may avert to the best of our ability the impending peril of clogged and rigid vessels.

In the examination of the living patient there are numerous ways in which the presence of arteriosclerosis may be detected. The method of palpation of the arteries is old; I am almost tempted to

say, as old as it is uncertain. The examination of ocular fundi gives an excellent index of arterial disease in many cases. Since an extensive study of the eyes in diabetic patients is at present being carried on by Dr. Waite and Dr. Beetham at the Deaconess Hospital, the results of this method of examination will not be touched on here, but left for their monograph. Roentgen-rays provide an excellent means of diagnosis of arteriosclerosis, particularly in the peripheral arteries, when accompanied by calcification. However, this diagnostic method can take no cognizance of atheromatous or other changes even though they may be very extensive, recording only the deposition of lime salts. One of the most extensive studies of this type is that by Rühl.[3] The recent article by Morrison and Bogan[4] illustrates very nicely the great help that the Roentgen-ray may give in the diagnosis of arteriosclerosis with calcification.

TABLE 25.—SIX HUNDRED AND FOUR ARTERIOSCLEROTIC DEATHS IN DIABETICS BY CAUSE AND AGE (BANTING ERA) COMPARED WITH ARTERIOSCLEROTIC DEATHS IN MASSACHUSETTS. (JOSLIN.)

Age at death, yrs.	Total deaths.	Types of arteriosclerotic deaths.				Total arteriosclerotic deaths.		Arteriosclerotic deaths in Massachusetts.
		Apoplexy.	Arteriosclerosis, gangrene.	Cardiac angina pectoris.	Nephritis.	No.	Per cent.	Per cent.
Under 30	77	...	3	4	...	7	9.0	4.5
30 to 39	35	...	3	2	...	5	14.3	16.3
40 to 49	49	1	4	5	3	13	26.5	27.4
50 to 59	149	7	17	35	15	74	49.6	39.0
60 to 69	203	18	39	57	11	125	61.5	51.6
70 to 79	79	8	21	15	3	47	59.5	61.5
80 to 89	12	2	2	5	...	9	75.0	67.3
90 . .	...	...	...	...	...	..	..	65.9
Totals .	604	36	89	123	32	280	46.3	36.7
Per cent	...	5.9	14.7	20.4	5.3			
Massachusetts .		9.4	3.6	18.2	5.6	..	36.7	

Our other means of diagnosis are clinical: The physical signs and symptoms of local circulatory deficiencies. Some of these are of definite value, such as the pain in claudication, the occurrence of gangrene, color changes, the presence or absence of pulsation in the vessels and local temperature. However, these do not directly concern the pathologist.

There are two main types of arteries: The elastic arteries, such as the aorta, the iliac and carotid arteries; and the muscular arteries, in which the development of the muscularis very often overshadows that of the elastic laminæ. This muscular type is encountered chiefly in the peripheral and the splanchnic arteries. The arterioles also are of the muscular type.

In non-diabetic individuals the vascular pathological changes that we encounter are fairly closely correlated with the different types of vessels. The atheromatous plaque is the characteristic arteriosclerotic lesion of the elastic arteries. This may present several forms, all of which are presumably related and represent various stages in the process of atheromatous degeneration.

According to Aschoff,[1] the first stage is the so-called atheromatosis of puberty, characterized by fine yellowish sub-endothelial streaks or spots, particularly about the orifices of the intercostal arteries. The plaques are translucent and slightly raised. The elasticity of the vessels is normal. Microscopic examination shows the swelling and loosening of the intercellular substance of the intima, chiefly in the deeper layers, with the deposition of minute fat droplets. These among the fibrillæ consist chiefly of cholesterol esters. The fatty infiltration is far more marked in the intercellular substance than in the cells themselves. As the process develops, more and more of the intima is involved, until finally the endothelium is reached. These changes are apparently reversible.

Aschoff calls attention to the increased knowledge of this lesion that the World War brought us through the study of large amounts of approximately normal material, particularly in young individuals. The frequency of atheromatosis was striking. He also mentions the decreasing frequency of the occurrence of atheromata as the food supply lessened with the greater duration of the war.

The next step is the development of true arteriosclerosis or atherosclerosis which is fundamentally the same. However, there has been a more marked swelling and hyaline change of the ground substance of the intima with infiltration of lipoids and new formation of fibrous tissue, which in turn becomes hyalinized. Beneath the hyaline connective tissue there may or may not be an enormous mass of atheromatous material. Finally, necrosis of the tissue cells occurs with decomposition of the cholesterol esters to the characteristic needle-shaped cholesterol crystals and fatty acids, which sooner or later combine with calcium. These calcium soaps become the calcareous or even bony plaques formed in the athero-

matous regions. As the plaque becomes larger and reaches nearer the surface the blood stream may sweep away portions of the pultaceous material, forming the familiar atheromatous ulcer. Aschoff emphasizes that the lipoid content of the plasma does not cause the atheromatosis but influences the character of the atheromatous plaques by determining the degree of fatty infiltration of the hyalinized ground substance.

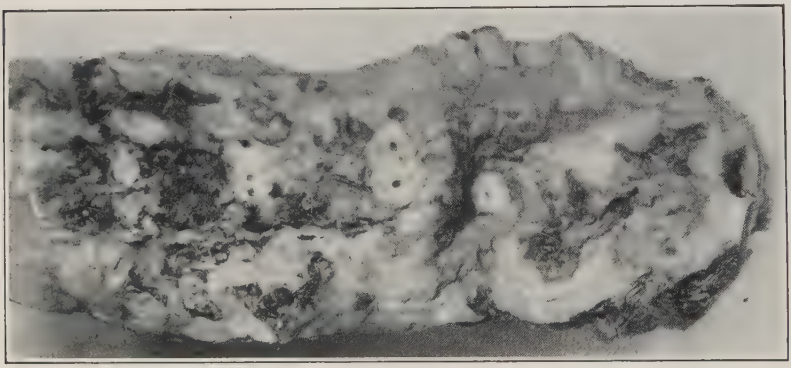

Fig. 54.—Portion of aorta from a diabetic male, aged sixty-seven years. Duration of diabetes unknown. Extremely marked arteriosclerosis of the atheromatous type.

The second great type of arterial change is that seen in the muscular vessels. Here medial calcification, the Mönckeberg type of sclerosis, predominates. This lesion is entirely distinct from the atheromatous process which we meet in the elastic vessels and is restricted to the muscular vessels. Intimal change is negligible and the lumen remains intact or is even actually widened. The initial change is the deposit of granules of calcium in the connective-tissue stroma about the muscle cells. This calcification gradually becomes more and more abundant, finally surrounding and causing atrophy of the smooth muscle cells. It is sometimes difficult to tell whether the particles of lime are outside or within the muscle cells, which may be necrotic. Any leukocytic reaction is extremely rare. Not infrequently organization of the calcified mass may take place with resultant formation of bone, which may even contain marrow in the more advanced cases. Through secondary intimal injury thrombosis may occur, as shown in Fig. 55.

There is little, if any, relationship between the occurrence of this type of arteriosclerosis and the atheromatous, although occasionally

the two forms may coëxist. In the smaller arteries there may be thickening of the intima with or without the deposit of lipoids. When this intimal change is at all marked one is justified in considering the possibility that the patient from whom the vessel was removed may be diabetic.

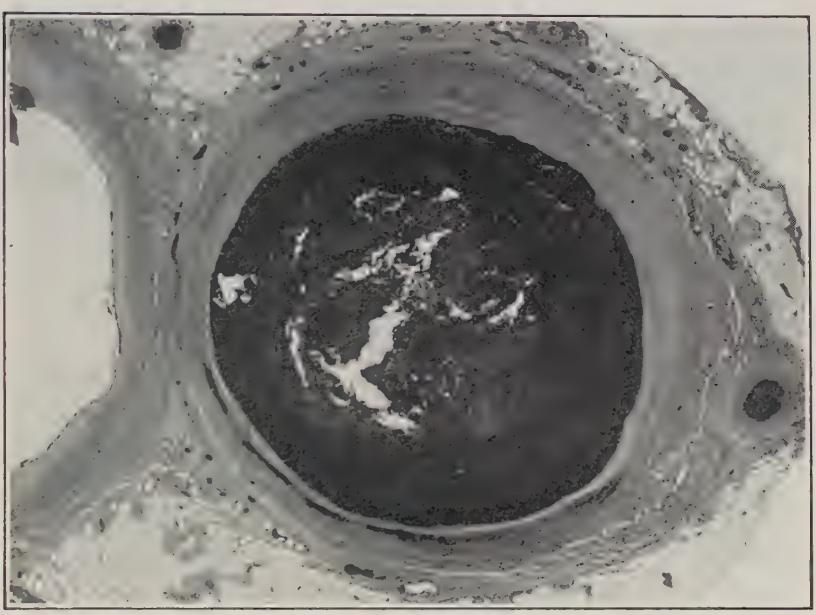

Fig. 55.—Femoral artery showing medial calcification or the Mönckeberg type of sclerosis. The dark mass filling lumen of the artery is a thrombus. Thrombosis is not infrequent in advanced cases.

The third great type of arterial change is that known as thromboangiitis obliterans, or Buerger's[3] disease. This type occurs in young adults. Here thrombosis, organization of the clot and subsequent partial recanalization of the thrombosed vessels are the outstanding features, followed by shrinkage of the walls and resultant reduplication of the elastic laminæ. Calcification is absent as is deposition of lipoids. There is usually a very sharp distinction between the fairly normal appearing adventitia and muscularis and the obliterated fibrosed lumen. An excellent example is shown in Fig. 56.

Still a fourth type of vascular change is met with in the smallest of the arteries and the arterioles, the so-called obliterative endarteritis. This usually appears as a hyaline thickening of the intima,

well exemplified by the hyaline change so frequently seen in the terminal arterioles of the spleen. Hyaline changes in the elastic laminæ are undoubtedly of great importance. Obliteration of the lumen may be practically complete.

In the diabetic individuals the atheromatous type of lesion is the outstanding one. The others may be present, but if there is one thing that should lead us to suspect an artery in a given case comes from a diabetic patient it is when we find the intimal type of involvement in the muscular arteries, either alone or superimposed upon the medial calcification.

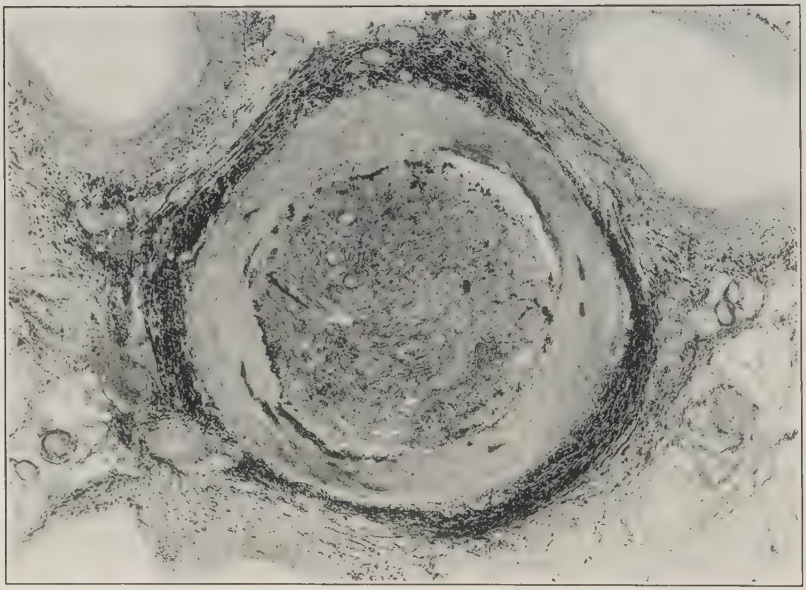

FIG. 56.—The anterior tibial artery from a case of thrombo-angiitis obliterans occurring in a non-diabetic. Note the granulation tissue and fibrosis involving the lumen with some recanalization.

In studying the lesions in the vessels on diabetic patients it is necessary to establish criteria for the presence of arteriosclerosis that would rule out any of the simple reversible or nutritional disturbances.

We have attempted to draw up criteria for our use at the Deaconess Hospital by which the reversible atheromatosis of Aschoff may be ruled out and only true arteriosclerotic lesions included. I feel almost all pathologists would agree to these.

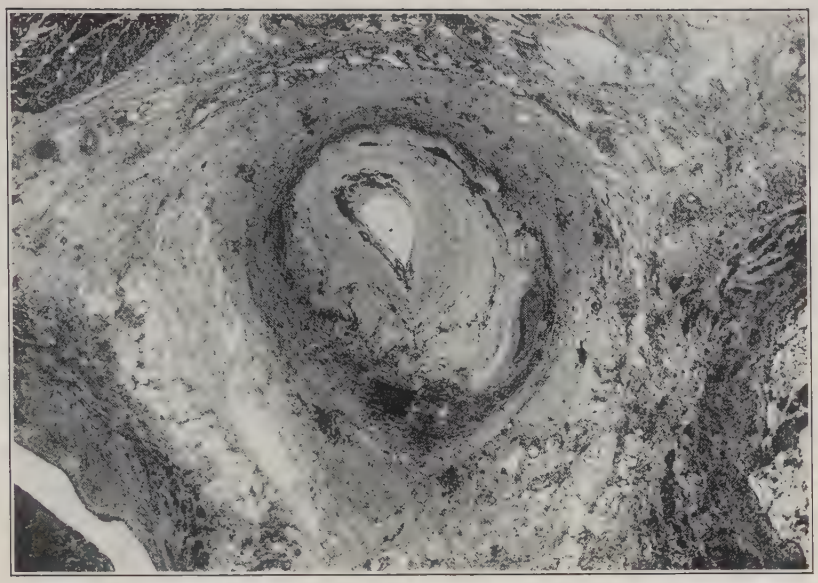

FIG. 57.—Arteriosclerosis involving the anterior tibial artery of the typical diabetic type. Note the marked intimal thickening. There is also a considerable degree of medial calcification. Hematoxylin-eosin stain. × 10.

FIG. 58.—Roentgen-ray photograph of the legs of a boy, aged fifteen years. Duration of diabetes six years. Showing the marked calcification of the tibial arteries.

Arteriosclerosis of the intimal type may be considered to be present if we have local thickening and hyaline change of the intima with lipoid infiltration, the presence of cholesterol crystals or the presence of calcified deposits. These changes are practically always accompanied by fraying or reduplication of the internal elastic lamina.

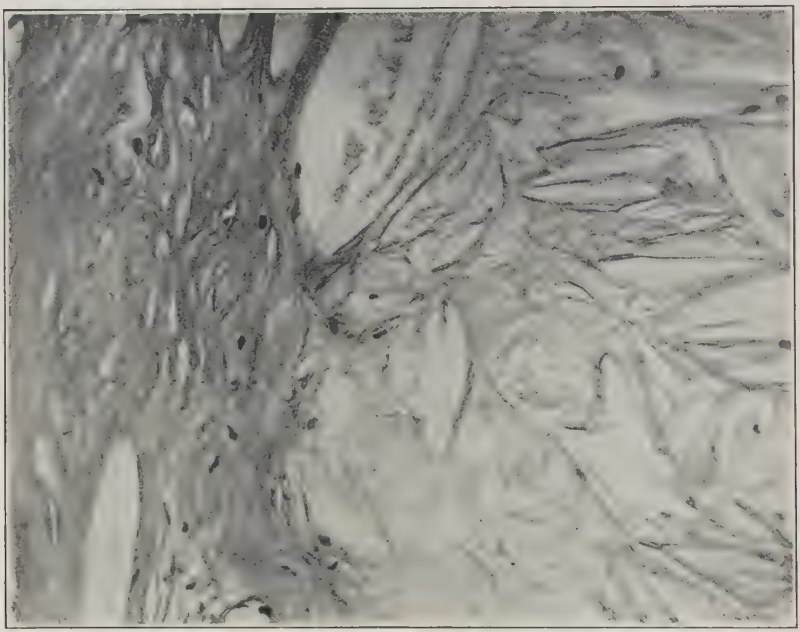

FIG. 59.—Masses of cholesterol crystals from thickened intima of anterior tibial artery. Male, aged sixty-one years. Duration of diabetes unknown. Intimal change is accompanied by a moderate amount of medial calcification. Eosin-methylene blue stain. × 375.

The medial type of sclerosis was considered to be present if there was either calcification or hyaline degeneration of the smooth muscle cells of the media.

Hyaline degeneration of the small arterioles may be diagnosed if the thickness of the intima has become more than twice normal.

In my series of 300 diabetic autopsies 72 deaths (24 per cent) were due to arteriosclerosis or tissue changes immediately secondary to that lesion. Since 80 cases of the series were under forty years of age, this high prevalence of arteriosclerosis as a cause of death is even more striking. Of the 23 cases of diabetes of fifteen years'

duration or over, 13, or 56.5 per cent, died from arteriosclerotic lesions.

TABLE 26.—INCIDENCE OF ARTERIOSCLEROSIS BY DECADES.

Age at death, yrs.	Total cases.	Arterio-sclerosis present.	Deaths due to arterio-sclerosis.	Total incidence of arterio-sclerosis.	Arterio-sclerosis absent.
0 to 10	9	0	0	0	9
11 to 20	23	7	0	7	16
21 to 30	19	10	0	10	9
31 to 40	21	18	1	19	2
41 to 50	36	29	6	35	1
51 to 60	66	48	17	65	1
61 to 70	65	30	35	65	0
71 to 80	19	7	12	19	0
81+	2	1	1	2	0
?	4	3	0	3	1
Total	264	153	72	225	39

TABLE 27.—ARTERIOSCLEROTIC DEATHS AMONG 300 DIABETIC AUTOPSIES.

Arteriosclerosis of vessels of:	No.	Per cent.
Heart	31	43.1
Extremities	27	37.5
Brain	8	11.0
Kidneys	4	5.6
Generalized	2	2.8
Total	72	100.0

The heart led all the other organs, with 31 of the arteriosclerotic deaths to its discredit. Of course, this is only a small proportion of the hearts showing the evidences of arteriosclerotic injury, as reference to Chapter IX will show.

Arteriosclerosis of the extremities, as exemplified by fatal gangrene, accounted for 27 deaths. On the other hand, cerebral manifestations of arteriosclerosis were responsible for only 8 deaths, one-ninth the deaths due to arterial change, and arteriosclerosis of the kidneys, although present in many cases, was fatal in only 4.

TABLE 28.—ARTERIOSCLEROTIC DEATHS AMONG 23 DIABETIC AUTOPSIES.
Duration of Diabetes, Fifteen Years or Over.

Arteriosclerosis of vessels of:	No.	Per cent.
Heart	9	69.2
Extremities	3	23.1
Brain	1	7.7
Kidneys	0	0.0
Generalized	0	0.0
Total	13	100.0

This marked prevalence of cardiac and peripheral arterial involvement in diabetic patients contrasts strongly with the frequency of cerebral and renal damage in non-diabetics. That this is no peculiarity of the present series is shown by Table 29, giving the site of fatal arteriosclerosis in 544 cases, from among 1756 fatal cases of diabetes.

TABLE 29.—LOCALIZATION OF TERMINAL ARTERIOSCLEROTIC LESIONS. (JOSLIN.[6])

Localization of arteriosclerosis causing death.	Incidence of localization to arteriosclerotic deaths.		
	Naunyn epoch, per cent.	Allen epoch, per cent.	Banting epoch, per cent.
Brain	17	18	13
Kidneys	23	14	11
Heart	37	41	45
Peripheral arteries	23	27	31

The relative immunity of the brain of diabetics to arteriosclerotic injury is due to the relatively small amount of hypertension in this group.

While atheromatosis and localized calcification of the intracranial vessels are not rare, the most frequent source of cerebral hemorrhage is rupture of a miliary aneurysm. These aneurysms are formed by distention of the weakened wall by the pressure of the blood, and this is the same force that ruptures them. Hence hypertension is a very important factor in the production of cerebral hemorrhage. In the larger intracranial vessels partial obliteration of the lumen through arteriosclerosis is relatively unimportant, owing to the abundant anastomosis supplied by the circle of Willis.

Table 30 from Joslin illustrates the low incidence of hypertension among diabetics. When hypertension does occur, it may be secondary to the vascular changes.

TABLE 30.—THE BLOOD-PRESSURE IN DIABETES. (JOSLIN.[7])

Period.	Age group, yrs.	Total cases.	Blood-pressure.									
			100 to 125.		126 to 150.		151 to 175.		176 to 200.		Above 200.	
			No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Before April, 1919	21 to 50	448	174	39	191	43	56	12	19	4	8	2
After April, 1919	21 to 50	356	161	45	147	41	35	10	10	3	3	1
Before April, 1919	Over 50	675	172	26	283	42	129	19	62	9	29	4
After April, 1919	Over 50	522	119	23	196	37	124	24	53	10	30	6

Wilder[8] reported in his series that "arteriosclerosis of considerable degree occurred in nearly all cases when the age of the patient exceeded forty years."

Taking the aorta as an index of arteriosclerosis, we find only 37 free from arteriosclerosis among the 235 which are recorded. Of these, 35 showed slight involvement, 61 moderate and 102 marked involvement. This tabulation includes cases of all ages, though naturally most lie in the older age groups. Possibly a few cases of atheromatosis of the presclerotic type may be included among the 35 cases showing slight involvement, but so far as possible this has been ruled out.

Taking the renal vessels as an index, the incidence of arteriosclerosis is less, as would be expected from the small number of deaths due to arteriosclerotic nephritis. Forty-nine showed a slight degree of either arteriosclerotic or chronic progressive (arteriosclerotic) nephritis, 47 showed moderate changes and only 11 showed marked.

TABLE 31.—INCIDENCE OF ARTERIOSCLEROSIS IN 300 FATAL CASES.

Arteriosclerosis of:	Slight.	Moderate.	Severe.	Missing.
Aorta	35	61	102	67
Kidney	49	47	11	106

The association of coronary sclerosis with gangrene is very striking. Fourteen cases showed both gangrene and infarcts of the heart, healed, fresh or both. Thus, 25.5 per cent of the 55 cases of gangrene occurred in conjunction with infarcts of the heart.

GANGRENE.

Gangrene is one of the most serious complications of diabetes, both from the nature of the lesion itself and from the wide path it opens to septic invasion of the body. Among these 300 fatal cases of diabetes, 55 cases of gangrene developed, and in 27 cases it was the primary fatal lesion. Eleven were accompanied by generalized sepsis, and there were 2 cases of gas gangrene.

TABLE 32.—FIFTY-FIVE CASES OF GANGRENE AMONG 300 DIABETIC AUTOPSIES.

	No.	Coma.	Generalized sepsis.	Gas gangrene.
All cases	55	10	11	2
Cases over 15 years' duration	9	0	2	0
Duration unknown	4	0	0	1

In a series of 36 legs, 17 toes and 1 arm amputated for gangrene and examined in this laboratory during a little over one year, all but 5 legs were from diabetic patients. In 8 of the diabetic patients more than 1 amputation was performed.

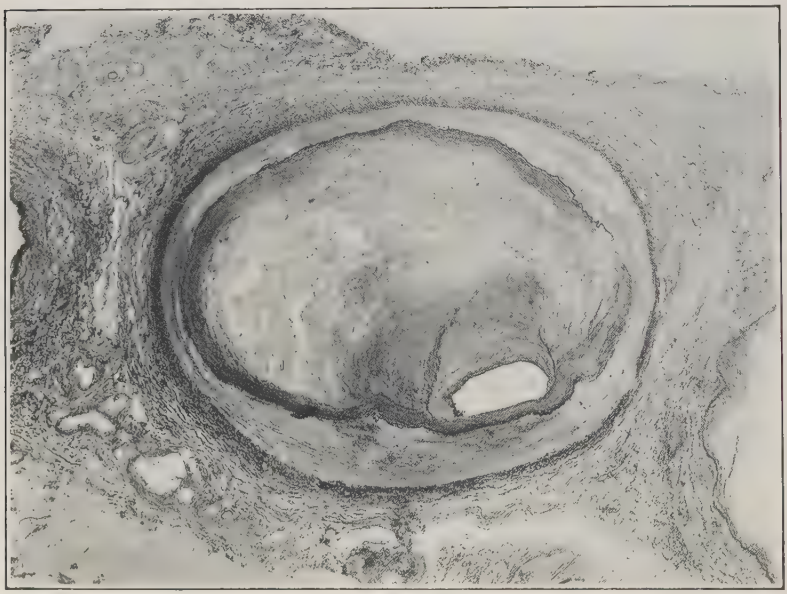

FIG. 60.—Almost complete occlusion of anterior tibial artery by intimal thickening. Note the elastic lamina still intact. At the bottom of the figure the media shows a slight amount of thickening and early calcification. The reduction in size of the lumen is very striking. Blood-pressure, 130/80. No. 28863. Male, aged seventy-two years. Duration of diabetes 4.3 years.

Arteriosclerotic or Senile Gangrene.—The vascular pathology in the 5 non-diabetic legs is worth considering. No. 225, a male, aged sixty-one years, showed no arteriosclerosis of the atheromatous type, but complete obliteration of the arterial lumen due to thrombosis and organization. The vessels of No. 1513, a male, aged fifty-five years, showed extensive medial calcification of the arteries and also thrombophlebitis.

No. 3456, a female, aged fifty-eight years, had a thigh amputation of her left leg for dry gangrene. The arteries were markedly calcified, with extreme involvement of the media. Their lumina were filled with loose connective tissue, free from lipoids, with occasionally a small amount of hemosiderin. Small recanalized lamina were present in some. Autopsy seven days later showed

general arteriosclerosis with coronary thrombosis as the immediate cause of death.

No. 3732, a right leg from a white male, aged seventy-nine years, showed dry gangrene of the toes. The larger arteries showed marked medial calcification, with thrombi partly organized in the lumina. In the smaller arteries the elastic lamina was heavily infiltrated with calcium.

No. 4104 was the right leg of a white female, aged eighty-nine years, with patches of dry gangrene involving the toes and heel. There was extreme calcification of the media, with marked fibrous thickening of the intima.

The important rôle played by medial calcification is well brought out in these cases. Even in the sections showing marked fibrous intimal thickening the orientation of the fibroblasts and collagen suggests that the fibrosis arose from points of particularly severe medial involvement, sweeping outward fanwise into the intima.

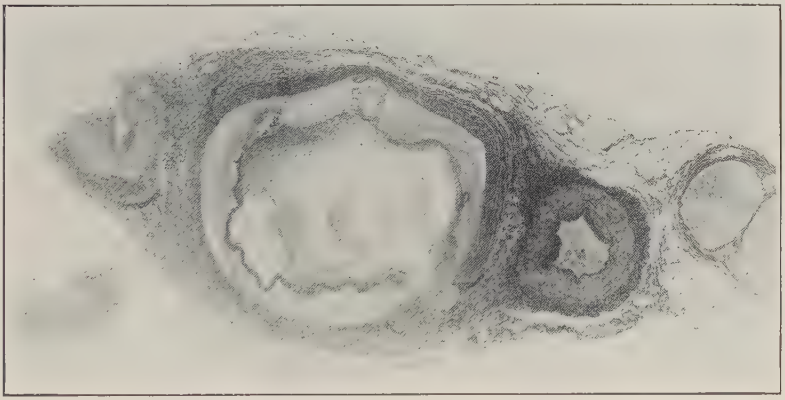

Fig. 61.—Lower portion of posterior tibial artery from same case as Fig. 60 showing complete occlusion by intimal proliferation and only slight involvement of media, some calcification being present.

Embolic Gangrene.—Gangrene due to embolic occlusion of the larger vessels is the same in diabetic as in non-diabetic persons. No. 438, an arm from a diabetic, aged sixty-one years, showed embolism and secondary thrombosis of the axillary artery. There was slight medial calcification, but no intimal change.

The youngest case of embolic gangrene in diabetes that I have seen occurred in Dr. Brigham's case.[9] Sudden gangrene of the left foot developed in a boy, aged nineteen years, who was in diabetic coma,

precipitated by pneumonia. In the article in which this case is reported, 52 others have been collected from the literature.

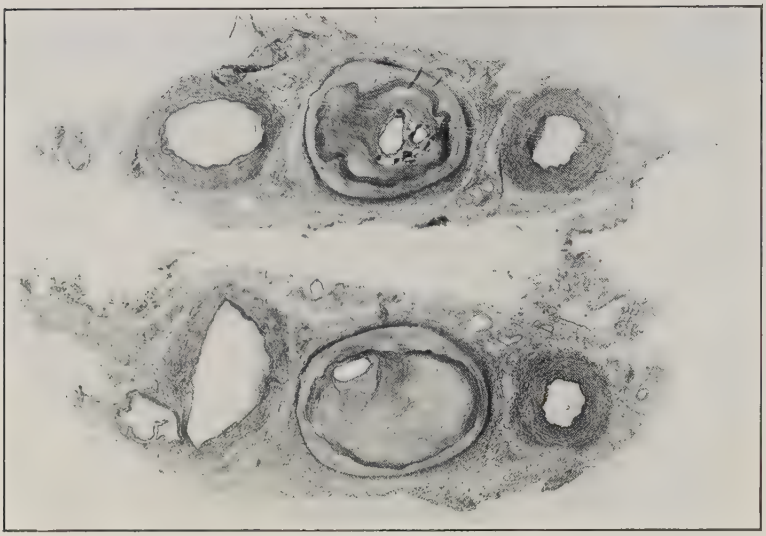

FIG. 62.—Low-power view of Fig. 60 in the lower portion of figure. Segment lower in artery shown in upper portion of figure. Note extreme narrowing of intima with very minute amount of lumen left. Almost no medial involvement.

Gas Gangrene.—Only 2 cases of fatal gas gangrene have been encountered in the present group. Since the infectious feature of this condition is the most important, it will be discussed more fully in Chapter X.

Diabetic Gangrene.—Numerous examples of diabetic gangrene could be selected to make a striking contrast to the cases described above. However, there are all stages of gradation between the two groups, and it is frequently impossible to tell from the vessels alone as to whether the gangrene is diabetic or non-diabetic in type. One particular difficulty is that many of the cases of gangrene in diabetic patients occur at the age when medial calcification is prevalent and diabetics have no immunity to this lesion.

There is one striking difference between arteriosclerotic and diabetic gangrene—one might almost use as synonyms for these dry and moist gangrene respectively. The final occlusion of larger arteries is usually sudden in the arteriosclerotic type, although the medial calcification, the primary pathological change, may have been present for years. However, this does not cause any gradual

narrowing of the lumen. Hence there has been no stimulus for the establishment of a collateral circulation and anemic necrosis results. McKittrick and Root[10] illustrate excellently the absence of collateral circulation. As they point out, many diabetics show this type of gangrene.

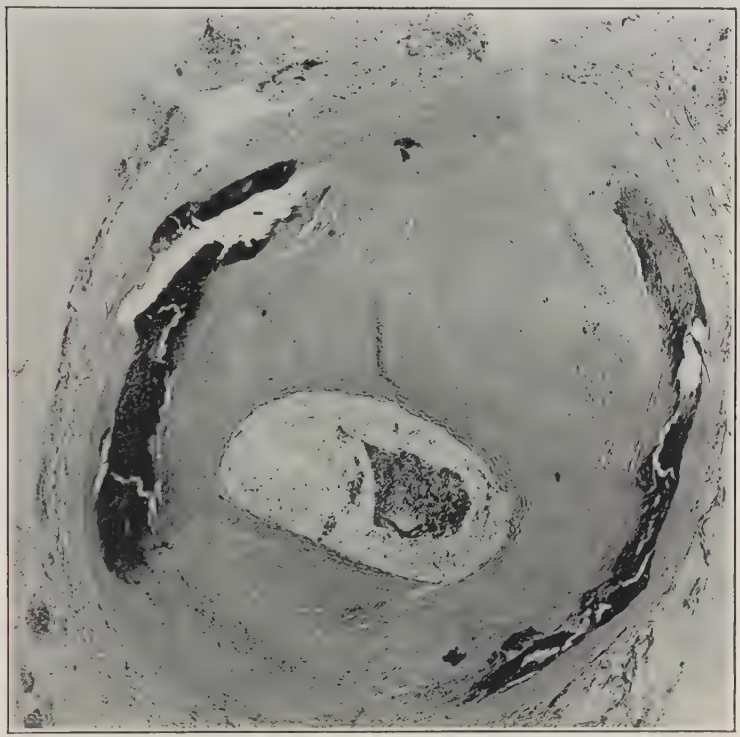

FIG. 63.—Extreme medial calcification and narrowing of lumen by intimal proliferation.

Arterial occlusion in the typical diabetic gangrene is a gradual process, at least at first—a progressive encroachment on the lumen of the artery by intimal thickening, not infrequently showing heavy deposits of lipoid. Hence, there is time for collateral circulation to develop. This is well shown in Fig. 64. While there may have been pain and disability during the process of readjustment, eventually a delicate point of equilibrium is reached where the combined blood supply from both main vessels and collaterals is just sufficient for the ordinary needs of the limb. Any unusual stress will tip the

balance. There will be insufficient blood supply to maintain life of the tissues under abnormal condition, too much to permit mummification. Moist gangrene results, and all too often leads to generalized sepsis.

FIG. 64.—Roentgen-ray of injected leg after amputation. Case No. 27117, aged seventy years. Diabetic gangrene. Very extensive collateral circulation present. Note occlusion of dorsalis pedis artery. (McKittrick and Root.)

In the past four years, gangrene caused only 1 in 11 diabetic deaths in Joslin's Clinic, as against 1 in 8 previously.

FIG. 65.—Early diabetic gangrene of foot and osteomyelitis. Case No. 37554. Aged seventy-four years. (McKittrick and Root.)

FIG. 66.—Gangrene due to embolic occlusion. (McKittrick and Root.)

On this basis we may say that the typical diabetic gangrene is preventable. True, the camel's back is bending, but the last straw can be withheld. Injury and particularly infection can be prevented. Dirt, ill-fitting shoes, carelessness, all simple, all inexcusable in properly taught patients (and only the diabetic with knowledge of how to care for his special hazards and disabilities may defeat the disease)—but nevertheless the causes of many cases of gangrene.

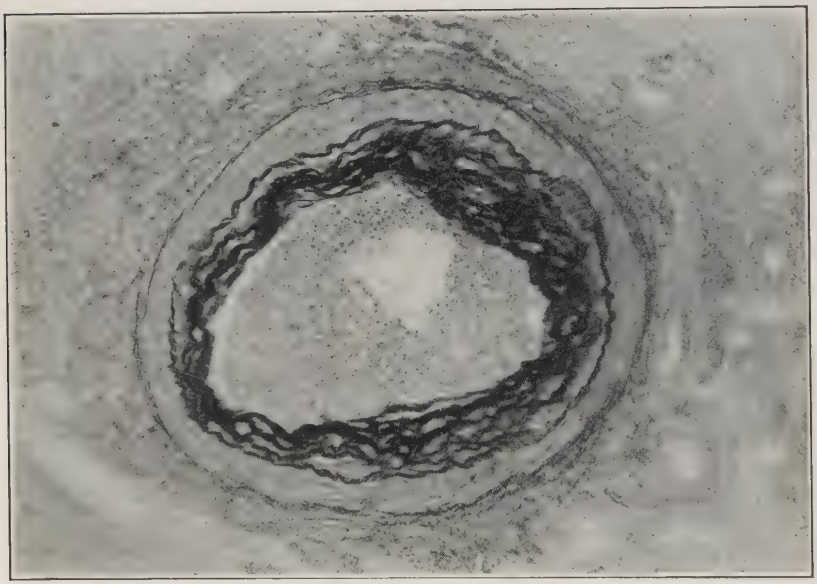

FIG. 67.—Weigert stain of kidney arteriole in arteriosclerotic nephritis showing great reduplication of elastica.

Specimen No. 2744 was a portion of knee and thigh amputated from the right leg of a male, aged sixty-seven years, whose diabetes had been present for at least 1.3 years. His left leg had been amputated by the Gritti-Stokes method in December, 1927. July 5, 1928, a palliative operation was done for gangrene of the right leg. During August he developed carbuncles, which were successfully treated by incision and drainage. Two transfusions were given. September 28, 1928, a Gritti-Stokes amputation was done on this leg. The media of the popliteal artery showed incomplete calcified rings. The lumen was completely occluded by loose connective tissue, tending toward concentric arrangement with scattered fat-filled

large mononuclear cells and several foci of cholesterol crystals with foreign-body giant cells about them. Scattered polymorphonuclear leukocytes were present in the adventitia and media.

Specimen No. 2276, from a male, aged sixty-one years, whose diabetes had been known for several years, was a right leg amputated above the knee. The little toe and adjacent dorsum and sole of the foot were black and firm. The adjacent tissue was swollen, bluish-red and crepitant. On cutting it, bubbles of gas escaped. The popliteal artery showed slight medial calcification. Its lumen was reduced to one-quarter by a large focus of cholesterol crystals in the intima, with fibroblastic proliferation and marked swelling of the intercellular substance of the intima. On the side most heavily involved the elastic lamina had disappeared. The arterioles showed marked hyaline thickening of the intima, which sometimes was four times the normal thickness.

Many other cases could be added, but these will serve to illustrate the type of intimal involvement which diabetes appears to transplant from the elastic to the muscular type of arteries.

THE ETIOLOGY OF ARTERIOSCLEROSIS.

One cannot help but feel that there must be some one factor bringing about the premature development of arteriosclerosis* in the diabetic organism, and modifying its appearance toward the intimal type no matter what arteries are involved. Its occurrence in young as well as old, the known existence of abnormally large amounts of lipoids, particularly of cholesterol in the blood stream of diabetics, the lipoid deposits so frequent in the disease, all lead one to believe that abnormal lipoid metabolism plays an important part. To prevent the great toll of disability and death that arteriosclerosis exacts, its cause or causes must be discovered.

Hypertension is not as prominent in arteriosclerosis of the diabetic type as it is in the non-diabetic type, and in view of the increased prevalence of arteriosclerosis in diabetics, it is probably an important factor in relatively few cases.

Moreover, atheromatous plaques are not infrequently found in the pulmonary artery and its larger branches in diabetic patients showing marked arteriosclerosis, a location where increased blood-

* In the following discussion arteriosclerosis of the atheromatous type will alone be considered.

pressure can play a relatively slight part, and where, in the absence of obstruction to the pulmonary circulation, arteriosclerosis is very rare.

Infection may be ruled out as a direct factor in the production of arteriosclerosis, other than in the definitely established syphilitic and rheumatic[11] types of arteritis. While a true arteritis is undoubtedly present in many vessels obtained from both surgical and postmortem diabetic material, this is always secondary to a septic process in the adjacent tissues. The bulk of the arteries from cases of diabetic gangrene that I have been able to examine histologically showed at one point or another an infiltration, frequently intimal, with polymorphonuclear or more rarely mononuclear leukocytes.

However, this infiltration is not restricted to the arteries, but may also involve the veins and lymphatics, and apparently can be traced to infection of soft parts. It is not unlikely that some of the intimal polymorphonuclear infiltration in the smaller arterioles represents an outward migration of the leukocytes in response to chemotactic attraction by the infected soft parts. Hence, though arteritis is not infrequently present, it is not in itself a cause of arteriosclerosis.

The most obvious common factor to all cases of diabetes mellitus is the disturbed carbohydrate metabolism. However, the cases with high blood sugar lived too short a time in the pre-insulin days to develop arteriosclerosis, and now insulin keeps the blood sugar fairly well within bounds. Joslin feels a blood-sugar level of 0.20 per cent is not harmful if the urine is sugar-free.

Excessive amounts of protein metabolites must also be considered, but it is doubtful if the protein the diabetic patient receives is sufficient in amount to be injurious. Certainly many heavy eaters of protein escape arteriosclerosis.

The well-known tendency of diabetic patients to have high blood lipoid, particularly cholesterol, the frequent occurrence of obesity in diabetic and prediabetic persons, all are strongly suggestive. When this is coupled with the prevalence of the atheromatous type of arteriosclerosis, it is impossible to disregard the presumptive importance of lipoid, and particularly cholesterol.

The chemical evidence of Windaus,[12] of Labbé and Heitz,[13] of Schönheimer[14] and of Miss Hunt and Mr. Lenherr, in the laboratory of the Deaconess Hospital, all point toward a definite relation between hypercholesterolemia and arteriosclerosis. Mere relationship, however striking it may be, is not enough. Otherwise every

time we eat a fat-rich meal, particularly eggs, from the cradle on, a bit of arteriosclerosis would be added.

Lipoids are not the first wave of the assault. They are the reinforcements that consolidate the gains made by the attacking force. The normal intima is not disturbed by fat, although occasionally the cells of the endothelium may phagocyte it. But given an abnormal intima, atheromata will develop in proportion to the amount of fatty substances present.

We may carry forward a step Aschoff's imbibition theory. In addition to "great physiological strain" tending to loosen the ground substance of the intima the diabetic has other factors.

The possible effect of a high-sugar concentration in producing swelling of the intimal ground substance through changes in osmotic pressure cannot be neglected. The concentration of the sugar in the connective tissue is not far from that in the blood, and the arterial wall should be no exception to the rule.

Fluctuations in sugar concentration occur more rapidly in the blood than in the tissues and so produce disturbances in osmotic pressure relationships.

An interesting confirmatory point is that biopsies of skin from a number of diabetics have been examined histologically for glycogen content. In those with high blood-sugar concentrations, the connective tissue of the corium is slightly edematous and basophilic, strongly resembling the change seen in the intimal ground substance in early arteriosclerosis. This change in the collagen is very similar to the swollen, basophilic form seen in many elderly persons, which Unna has called "collacin."

The development of acidosis may also tend to cause swelling of the intercellular substance of the intima. As Joslin has pointed out, the ketogenic diet being used in the treatment of epilepsy is producing a prolonged low-grade acidosis. If these cases are carefully followed, and a high concentration of blood lipoid found to be present, they should develop arteriosclerosis, provided acidosis alone does render the intimal ground substance more permeable.

Once the permeability of the intimal ground substance has been increased, the rest of the process is easy to follow. Lipoid-laden plasma penetrates into the vessel wall, and the droplets of lipoid remain behind to accumulate gradually and form the atheromatous plaque.

If this hypothesis be true it is as important in attempting to prevent the development of arteriosclerosis to maintain the blood

sugar within normal limits and to prevent the development of acidosis as it is to keep down the level of blood lipoid.

One very important factor in any consideration of arteriosclerosis in diabetes is the change that dietary treatment has undergone in the past fifteen years. The foundation for clinically demonstrable arteriosclerosis is laid months or years before it becomes manifest. Our sclerotic diabetics of today are reaping the harvest sown long before of inadequate treatment or neglect of the diabetic condition.

Joslin[15] summarizes the stages of treatment through which his patients have passed. The average daily diet was:

In 1915–1916: Carbohydrate, 26 grams; protein, 54 grams; fat, 76 grams.

In 1916: Carbohydrate, 43 grams; protein, 60 grams; fat, 82 grams.

In 1916–1917: Carbohydrate, 43 grams; protein, 60 grams; fat, 90 grams.

In 1923: Carbohydrate, 71 grams; protein, 58 grams; fat, 123 grams; with 13 units of insulin.

In 1927: Carbohydrate, 96 grams; protein, 60 grams; fat, 113 grams; with 21 units of insulin.

In 1930: Carbohydrate, 125 grams; protein, 63 grams; fat, 92 grams; with 23 units of insulin.

In other words, the patients are steadily approaching a balanced, normal diet. With each progressive step, some of the abnormal factors that may tend to produce arteriosclerosis are being reduced. While it is yet too soon to say, nevertheless the hope is justifiable that today the only diabetic to develop premature arteriosclerosis may be the neglected diabetic.

Arteriosclerosis is so prevalent that it may be considered almost a physiological accompaniment of old age. The absolute prevention of arteriosclerosis in diabetic patients is an ideal that will probably never be attained; the prevention of premature arteriosclerosis is attainable. The diabetic has not only more than his share of arteriosclerosis, but it falls to his lot ten or twelve years earlier than to the non-diabetic. This premature arteriosclerosis must be prevented.

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CHAPTER IX.

THE HEART.

A NATURAL sequel of the prevalence of arteriosclerosis in diabetic patients is the very frequent occurrence of myocardial injury due to coronary disease. A striking proportion of diabetic patients die of cardiac injury with or without coronary occlusion and infarction. While in the interpretation of the severity of lesions in chronic vascular myocarditis the personal equation may enter, some individuals regarding a given degree of fibrosis as more severe than others would, nevertheless there are four unequivocal lesions concerning whose interpretation there can be no question. These are: (1) A fresh infarct of the heart; (2) a healed infarct of the heart with or without aneurysmal dilatation; (3) rupture of the heart which is practically always due to infarction; (4) coronary occlusion.

The statistics of infarction are widely variable and depend somewhat on the type of practice from which the material is drawn. Thus, Benson and Hunter,[1] in the coroner's service at Portland, Ore., encountered 72 cases of infarcts and cardiac aneurysm in 1750 autopsies. Obviously any series of coroner's cases is markedly weighted by a high proportion of sudden deaths, and here, of course, coronary disease with varying myocardial changes ranks high. Among the 72 cases there were 46 recent infarcts, 11 healed infarcts, 18 cardiac aneurysms and 14 ruptures of the heart.

TABLE 33.—AGE DISTRIBUTION. (DAVENPORT[4].)

Age, yrs.	Total data.
"Aged"	30 (4.4 per cent)
80 to 90	58 (8.4 ")
70 to 80	195 (28.4 ")
60 to 70	217 (31.6 ")
50 to 60	92 (13.4 ")
40 to 50	49 (7.1 ")
30 to 40	25 (3.6 ")
20 to 30	8 (1.2 ")
10 to 20	8 (1.2 ")
1 to 10	5 (0.7 ")
Total	687

In hospital practice, however, the prevalence is very different. Thus Krumbhaar and Crowell[2] found only 7 cases of rupture of the heart among 16,000 postmortem examinations at the Philadelphia General Hospital, and Meyer[3] reported only 7 among 13,000 postmortems at Munich. Davenport,[4] bringing up to that date (1928) Krumbhaar's[2] report added 92 cases of rupture of the heart to the 654 cases previously collected, bringing the total number

Fig. 68.—Heart showing extreme myocardial degeneration secondary to vascular disease. An example of marked chronic vascular myocarditis. Non-diabetic.

in the medical literature up to 746. Davenport in analyzing the total number of reported cases of rupture of the heart gives the table (page 142) for those cases where the age distribution is known. The great preponderance in the later decades is strikingly shown. Presumably some of the cases in younger individuals are primarily due to abscesses, toxic injury and so forth rather than to infarction. In my short series of 282 diabetic autopsies in which the heart was

carefully examined there are 3 instances of rupture of the heart. In 1 of these cases the rupture was through the interventricular septum.

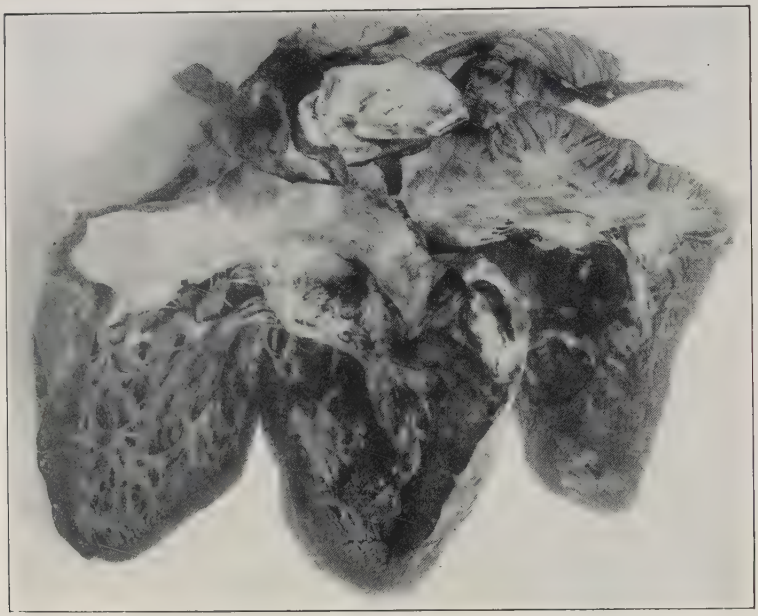

Fig. 69.—Heart showing healed and fresh infarcts. Note adherent thrombus in left ventricle. Female, aged fifty-nine years. Duration of diabetes fifteen years.

If we take Benson's series of 1750 autopsies as a fair index of the prevalence of cardiac infarction, containing as it does many cases of sudden death, and being if anything weighted in favor of the occurrence of an abnormally large number of infarcts, his 72 cases of infarction are relatively few compared with the 35 cases of infarction encountered in our series of 282 hearts from diabetic postmortems. In other words, his series, which in all probability included a few diabetic cases, showed an incidence of only 4.1 per cent, whereas in this series of diabetic autopsies there is an incidence of 12.4 per cent.

Ophüls,[5] in 3000 autopsies, of which 34 were on diabetic patients, found 18 cases of recent infarct and 8 of healed infarct. Seven cases showed aneurysms of the left ventricle, and in 2 the aneurysmal sac had ruptured.

The youngest death from cardiac infarction included in my series

of autopsies is a patient of Dr. Joslin, Case No. 1794. When twenty-five years of age diabetes developed. Under insulin treatment she had permitted her weight to increase from 67 to 135 pounds. At the age of thirty-three years, eight years after the onset of diabetes, she developed intense precordial pain after breaking diet. Death occurred in a few hours after several Cheyne-Stokes attacks. At autopsy she showed fresh infarction of the

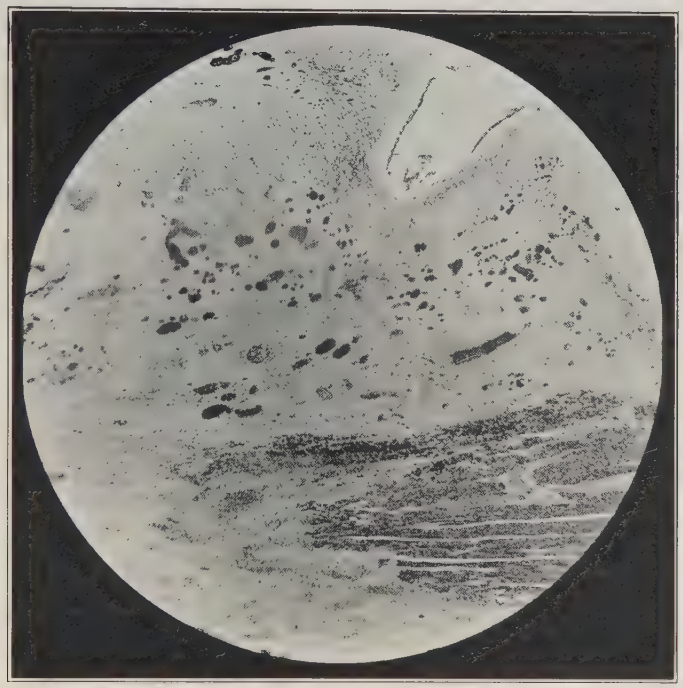

FIG. 70.—Margin of fresh infarct of heart from case U25-22. Female, aged thirty-three years. Duration of diabetes eight years. Note hydrops of muscle fibers adjacent to endocardium, which is still apparent in infarcted area. Phosphotungstic acid hematoxylin stain. × 36.

apex of the left ventricle and the interventricular septum. The left coronary artery was practically completely occluded, barely admitting a horsehair in its first portion. The right coronary artery showed numerous atheromatous plaques. Both of the coronary orifices were surrounded by atheromata which extended down on the endocardium beneath the aortic ring. The aorta showed extensive arteriosclerosis of the atheromatous type.

A typical death from angina pectoris occurred in Case No. 4079, under the care of Dr. Joslin, a girl whose diabetes had developed four and a half years before her death, at the age of twenty-two years. She had had occasional attacks of pain over the heart while walking and in the week just before her death had frequently complained of it. Her death occurred suddenly with the typical symptoms of angina while riding in an automobile. Her blood-pressure had been 120 mm. systolic and 90 mm. diastolic. The Wassermann reaction was negative, and there was no history of rheumatic fever or chorea. Unfortunately an autopsy was not obtained.

Strauss[6] reports Joslin's Case No. 2703, who died at the age of twenty-two years with coronary thrombosis. In 1920, at the time of the onset of his diabetes, eight and a half years before death, the Wassermann reaction was negative, and systolic blood-pressure was 118 mm. and diastolic was 75 mm.

The occurrence of infarcts and coronary occlusion in the present series are summarized in Table 34.

Table 34.—Incidence of Infarcts of Heart and Coronary Thrombosis in 282 Diabetic Autopsies.

	Fresh.	Healed.	Fresh and healed.	Total.	Coronary thrombosis without infarction.
Number of cases . .	9	18	7	34	2
Av. age, yrs. . . .	59	63.7	61.1	..	66
Av. duration, yrs. . .	11	12.5	12.4	..	?

Of the 9 cases of fresh infarct of the heart, the average age was fifty-nine years and the average duration of the diabetes was eleven years. Of the 18 cases with healed infarct the average duration was 12.5 years for the diabetes and the average age was 63.7 years.

Seven cases had weathered one or more myocardial infarcts before the one that proved promptly fatal. On the other hand, 2 cases died of coronary thrombosis, without time for the development of myocardial infarctions, although diffuse scarring of the myocardium indicated prolonged malnutrition due to arterial disease.

That diabetes is not merely an incidental feature in these cases is illustrated by the duration of the diabetic process, long antedating the cardiac condition. The average duration is twelve years, thus giving ample time for the abnormal metabolic conditions to affect the vessels. Cases treated with insulin from the onset of their diabetes may perhaps avoid this cardiac disability.

Levine,[7] in a group of 145 cases of coronary thrombosis, found 34

cases, or 23.7 per cent, with glycosuria or a previous history of diabetes. Over one-third of the diabetic cases (12) were females, whereas only one-fifth of the non-diabetic cases were females. In my series, of the total number of infarcts of the heart, 41 per cent occurred in females, and in cases where the immediate cause of death was infarct of the heart or coronary occlusion 42 per cent occurred in females. He states that "among the distinct disease entities that are etiologically related to coronary thrombosis, diabetes is second in importance only to a previously existing hypertension." In certain of the cases he feels that the glycosuria may be of a transient emotional type secondary to the attack.

However, if diabetes stands out so prominently in the general run of cases of coronary thrombosis the importance of this lesion for the diabetic patient is very obvious.

Levine[7] states the lesion is very rare in those under thirty years of age. He had no such cases in his group, and only 3 below forty years of age. However, I have cited above 2 cases of death from coronary disease in diabetics occurring at twenty-two years of age.

The average age at death in my series is greater than in Levine's, 62.4 years as against 57.8 years for his entire group, and 58.1 years for his diabetic group.

Nathanson,[8] in reviewing 100 diabetic autopsies, found extensive coronary disease in 52 per cent of diabetics above fifty years of age, as against 8 per cent in general autopsy material.

When we consider chronic vascular myocarditis, criteria are difficult to establish. However, scattered diffuse scarring of the musculature, chiefly perivascular, and barely visible in gross, was considered slight. Possibly these fine scars might be regarded as physiological rather than pathological. They are encountered very frequently in the hearts of elderly persons, non-diabetics as well as diabetics. A moderate degree of chronic vascular myocarditis was diagnosed when fine diffuse scarring was visible to the naked eye and when the microscope revealed frequent small foci of fibrosis. The presence of generalized fibrosis, both gross and microscopic, was considered as evidence of a marked degree of myocarditis.

Fairly closely paralleling these changes, so far as severity is concerned, and of course underlying them, are the changes in the coronary arteries. Here again three grades of involvement are considered:

1. Slight; scattered atheromata or fibrous thickening of the intima with but slight narrowing of the lumen.

2. Moderate; scattered atheromata with or without calcification or fibrous thickening of the intima, the lumen reduced not over one-third.

3. Marked; numerous atheromata, usually with some calcification, or fibrous thickening of the intima, the lumen reduced more than one-third. Actual occlusion may or may not be present.

Table 35.—Chronic Vascular Myocarditis and Coronary Disease in 282 Diabetic Autopsies.

	Vascular myocarditis.	Coronary sclerosis.
None	161	146
Slight	43	27
Moderate	26	45
Marked	15	52
Total	245	270
Data missing	37	12

In 49 cases of diabetes reported by Wilder,[9] in which the heart was examined at autopsy, 17 showed moderately severe or severe sclerotic changes in the coronary arteries and almost all of these cases showed gross injury to the myocardium, although in most of them there had been no symptoms of angina pectoris during life.

Clinically angina pectoris is more frequent the longer the duration of diabetes. In 209 cases of angina pectoris to be reported by Root, 38 had their onset before the age of fifty years. Forty per cent of the 209 cases were in females. The relatively short duration of life after the onset of angina pectoris in a diabetic is well explained by the severity of the coronary disease and myocardial change found at autopsy.

The occurrence of hypertrophy of the heart is not infrequent as is shown by Table 36.

Table 36.—Weights of the Heart in 282 Diabetic Autopsies.

	0 to 350 gm.	350 to 500 gm.	500+ gm.
Number	194	73	15

Three hundred and fifty grams was considered as the upper limit of the normal heart. Those weighing over 500 grams were considered markedly hypertrophic.

In the coronary arteries as in other arteries of the diabetic patient, intimal changes of the atheromatous type predominate. The involvement is not uniform; an artery may be almost completely occluded at one point and relatively normal at another. As else-

where, the atheromatous deposits tend to become calcified, and the arteries may become of pipe-stem character or show spots of cal-

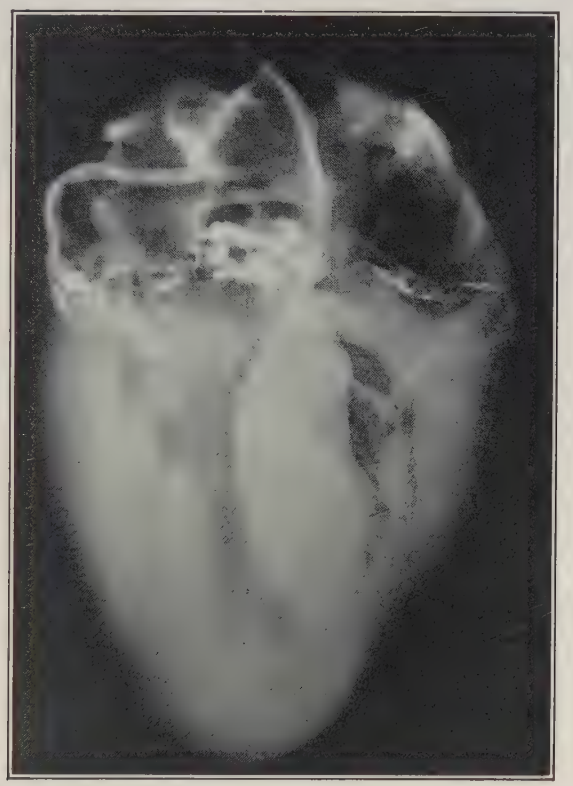

Fig. 71.—Roentgen-ray of heart from case of infarction and coronary thrombosis. No. 5142. Male, aged sixty-one years. Duration of diabetes one and a half years. Note the marked calcification of the coronary vessels. Also the hypertrophy of the heart as shown by the Roentgen-ray. The weight was 520 gm.

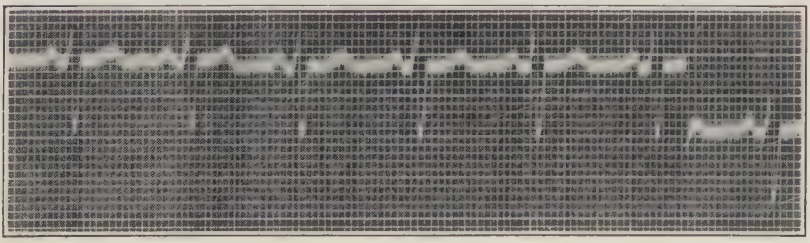

Fig. 72.—Electrocardiogram (Lead II) of heart shown in Fig. 70.

cification. Roentgen-ray examination* of the excised heart demonstrates the calcification well, as shown in Figs. 71 and 73. In the living body this method is not of value.

In addition to the atheromatous type of involvement, fibrous thickening of the intima frequently occurs.

Embolism of the coronary vessels was not encountered in this series.

While the correlation between coronary arteriosclerosis and that elsewhere in the body is fairly close in the diabetic patient, there are wide discrepancies at times, just as is found in non-diabetics.

FIG. 73.—Roentgen-ray of heart from Case No. 4996. Male, aged seventy-six years. Duration of diabetes thirty years. Infarct of heart with rupture. Note calcification of right as well as left coronary arteries.

Comparative studies of the electrocardiogram and the postmortem findings in the heart are being carried out by Dr. H. F. Root at this

* Performed by Drs. L. B. Morrison and I. K. Bogan.

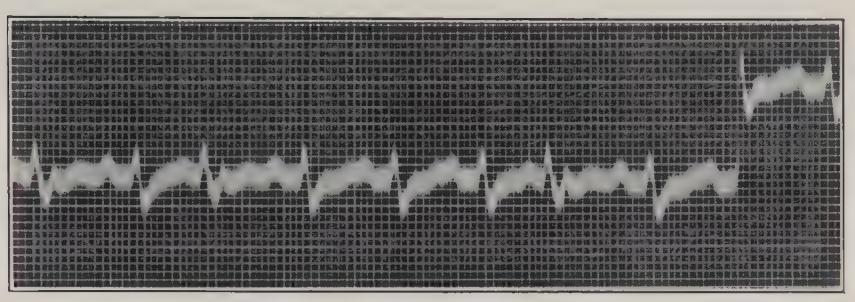

FIG. 74.—Electrocardiogram (Lead II) of No. 6778. Male, aged sixty-seven years. Duration of diabetes twenty years. Heart showed coronary thrombosis and both fresh and healed infarcts.

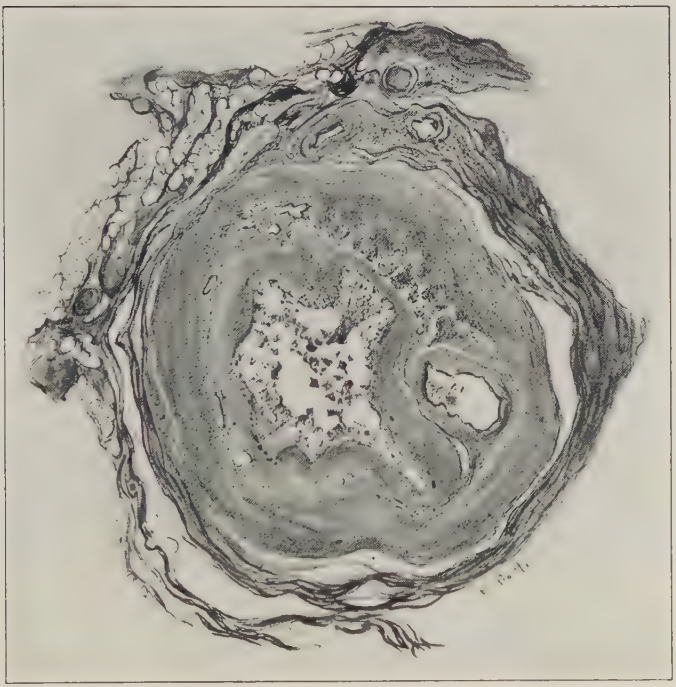

FIG. 75.—Drawing of left branch of coronary artery from a heart showing marked coronary sclerosis with calcification and occlusion, and a healed infarct of the heart. The organ weighed 510 gm. Note extreme involvement of intima. Apparent lumen in the center is due to large mass of fat and cholesterol crystals which has been dissolved out in the process of preparing the section. Male, aged fifty-seven years. Duration of diabetes 8.7 years. Hematoxylin-eosin stain. × 24.

hospital on a series of diabetic patients at the present time. Examples of the electrocardiographic tracings from 2 cases of coronary thrombosis are shown in Figs. 72 and 74.

Another serious myocardial injury not infrequently encountered is that of multiple abscesses. In cases as prone to sepsis as those of diabetes it is not remarkable that we should find in this series 5 cases of multiple abscesses of the myocardium, all of which were associated with multiple abscesses elsewhere in the body.

Diffuse pericarditis was a cause of death in 1 case, and was accompanied by coma in 2 other fatal cases. In 2 additional cases healed pericarditis of the chronic adhesive type was found. Thus 5 of the cases showed evidence of severe past or present pericardial inflammation.

FIG. 76.—Large abscess of the heart from a case of carbuncle with Staphylococcus aureus septicemia and numerous abscesses involving heart, liver and kidneys. Male, aged fifty years. Duration of diabetes twenty-three years.

In Chapter V the increased amount of glycogen in the diabetic heart was discussed briefly and attention was drawn to the tendency of the glycogen to be deposited in particularly large amounts in the fibers about the margins of infarcted or fibrosed areas, presumably indicating that the muscle fibers at this point were not able

to utilize so fully as those elsewhere the amount of glycogen deposited in them. Glucose, and of course its stored form, glycogen, is an absolute necessity for the heart muscle, and this storage of glycogen in the heart muscle fibers perhaps represents an effort of the diabetic organism to tide this important organ over any period of deficit in utilizable carbohydrate. Glycogen apparently exerts no deleterious effect through its presence.

Joslin, among others, has stressed the danger of suddenly reducing the carbohydrate in elderly individuals whose hearts are presumably somewhat diseased. If the muscle has been injured, the heart may not be able to weather the shock of sudden reduction of the carbohydrate supply.

A high blood-sugar level is not in itself injurious to the heart muscle, although Blitzsten and Schram[10] were able to find slight changes in the electrocardiograms of diabetic patients who showed no clinical evidence of cardiac pathology. Notching of the main deflection of the curves they felt occurred more frequently in diabetic than in control non-diabetic patients. They also found a greater amplitude of deflection, which paralleled roughly the increase in blood-sugar concentration. These increases in amplitude were produced experimentally in dogs by raising the amount of blood sugar, although there was no definitely quantitative relationship.

In view of the marked susceptibility of diabetic patients to infection, and the relative frequency of terminal septicemias, the rarity of bacterial endocarditis and valvular lesions is very striking.

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CHAPTER X.

DIABETES AND INFECTION.

Infection was the cause of death in 126 of these 300 fatal cases of diabetes. Tuberculosis and syphilis are omitted from this number, only the acute infections being considered. Twelve additional deaths were due to tuberculosis and 2 to syphilis. Moreover, a number of cases of gangrene are included, only those cases being considered where generalized sepsis or gas gangrene was the cause of death. Pneumonia was responsible for more deaths than any other infectious condition. There were 18 deaths from bronchial pneumonia, 6 deaths from lobar pneumonia and 16 from pneumonia complicated by coma.

Just as arteriosclerosis is the bugbear of the diabetic who is doing well, so infection is the fear of the diabetic who is doing poorly. The more severe the diabetes, the more susceptible he is to infection. Once a diabetic is infected his diabetes becomes far more severe. At the risk of becoming wearisome I will repeat once more that sepsis is the greatest foe of insulin.

Whether or not we can translate to man the result of the experiment of Rosenthal and Behrendt,[1] who found that fresh pus mixed with insulin abolished the insulin effect when it was injected into rabbits, nevertheless clinical observation has long shown that there is a marked increase in the severity of the disease during infection. As Joslin[2] states, "Insulin will not maintain a sugar-free urine during an active infection unless given in very large doses." Moreover, when these large doses are given there is the constant fear that with sudden recovery an insulin reaction may result.

Inasmuch as many cases of the acute infectious diseases show central or focal necroses of the liver or an acute tubular nephritis, so it is reasonable to suppose that other parenchymatous organs are acted on as well. Particularly where the pancreas of the diabetic is just on the ragged edge, its islands barely producing enough insulin to keep the organism going and needing to be helped out with either dietary control or extraneous insulin, it is obvious that any very slight infectious process or toxemia may be sufficient to injure the island cells. Thus, the already too delicate balance that is being maintained is overthrown.

I have seen this toxic injury to the islands in a number of instances, both in non-diabetic and diabetic patients. One of the most striking cases is that of a non-diabetic patient who died from lobar pneumonia. I[3] had the opportunity of studying this case, A15-16, while in Dr. Mallory's laboratory. Most of the cells in the islands of Langerhans were necrotic or showed some evidence of injury. There were, as well, numerous mitotic figures, sometimes as high as seven in a section of a single island, showing that there had been serious toxic damage. It is quite possible that cases such as these may give the clue to the transient glycosurias that occasionally appear in non-diabetic patients in the course of severe acute infections.

As I have previously suggested, it is perfectly reasonable to explain the severe drop in sugar tolerance noted in diabetic patients during acute infection in this same way. The one hopeful feature is that the diabetes is not made permanently worse, or rather the sugar tolerance is not kept at the same low level to which it is forced during the course of the infection. The quick recovery of the diabetic patient after the infection has gone is very striking indeed, suggesting that if the effect is on the insular epithelium it stops short of actual cell necrosis.

Of course the assumption is perfectly reasonable that the islands of Langerhans are not actually injured by the infectious process or its toxic products but that the effect is exerted elsewhere, perhaps on the insulin in the blood stream or perhaps in the tissues generally. Be that as it may, the fact remains the same that there is no reason to consider the diabetic organism as differing fundamentally from the normal and that, therefore, we are justified in transferring to the case of the diabetic the observations which have been made in the non-diabetic patient.

Graham[4] cites 7 cases of coma, 5 of which were fatal, in all of which infection was present. Five went into coma before the presence of infection could be diagnosed clinically. He advances three hypotheses to explain the lowered tolerance in the course of infections: (1) A direct effect on the β cells; (2) increase in metabolism due to the infection; (3) destruction of insulin or neutralization of it by products of the infectious process.

Six cases of fatal coma recently reported by Bayer[5] were all complicated by infection or gangrene.

The types of infection vary, but pneumonia and pyogenic infections stand out above all others.

Pneumonia was the most frequent fatal infection, being responsible for 40 deaths. Eighteen cases were of uncomplicated bronchial pneumonia and 6 of lobar. Sixteen fatal cases of pneumonia precipitated or were complicated by coma. One death was due to empyema.

To protect the diabetic against pneumonia there is relatively little that we can do except for maintaining his diabetes in as favorable a condition as possible. If anything, it is necessary to be overcareful with regard to colds and upper respiratory tract infections, in the hope of checking them before pneumonia may have an opportunity to develop.

After pneumonia the pyogenic infections are the most important, particularly those of the staphylococcus and the streptococcus groups. An intact skin is essential to a diabetic patient, for it is his best safeguard against infection. Blisters and scratches that would be insignificant to the normal person must be carefully guarded from the access of bacteria. Even organisms which ordinarily are of very low virulence are capable of setting up severe infections. Thus Staphylococcus albus is ordinarily considered of little significance and, indeed, if found in the blood culture is generally dismissed as a contaminant, yet it may be an extremely dangerous organism to the diabetic, responsible for pyemia and multiple abscesses just as in certain cases in children it may be responsible for osteomyelitis.

Through long clinical experience it has become obvious that when one encounters a case of stubborn furunculosis diabetes should be almost automatically suspected.

The diabetic skin is fertile soil for the pyogenic bacteria. The carbuncle with its tendency to develop septicemia with the subsequent establishment of multiple abscesses is one of the most dangerous types of cutaneous infection. Since these organisms are always present in the skin waiting for an opportunity to find their way into the subcutaneous tissues every break in the skin must be regarded as a potential source of danger and meticulously cared for until it has completely healed over. Ordinary cleanliness is, of course, of tremendous importance in both reducing the number of organisms present on the skin and in keeping in check their opportunities for entering wounds.

Pyogenic infections caused 33 deaths, 5 of which were secondary to gangrene and 9 were complicated by coma. In few cases aside from the fulminating osteomyelitis of children have I seen as widespread distribution of abscesses as that found in these cases.

Except for their extent and tendency to become generalized, furuncles and carbuncles in diabetic patients differ in no regard from those in non-diabetics.

Infection and gangrene are a particularly dangerous combination to the diabetic. Infection is not only a frequent complication of gangrene due to the low resistance of the undernourished and necrotic tissue, leading frequently to the establishment of generalized sepsis, but it may be the underlying cause as well. Even a low-grade infection may be sufficient to overcome the narrow factor of safety barely maintained in the diabetic leg with arteriosclerosis of the diabetic type and result in the establishment of the gangrenous process.

Autopsy No. 7104 illustrates very well the danger of infection and gangrene. The subject was a white male, aged fifty-eight years, who had been a fairly mild diabetic for twenty-five years. For the past four years he had taken insulin intermittently. One year before admission to the hospital he had had a sore on his left foot which finally healed. Three months before admission he stepped on a tack with his left foot, which made little trouble for ten weeks. October 15, 1929, a palliative amputation of the left lower leg was done. The vessels showed marked intimal and medial sclerosis. Streptococcus hemolyticus was found in the wound and in the blood stream. His condition continued poor. A blood culture, October 24, was negative. November 13, a thigh amputation was done. The vessels were markedly calcified, showed much intimal thickening and some acute arteritis. The stump became septic, and his condition grew steadily worse. Death occurred, December 11. The immediate cause of death was Streptococcus hemolyticus sepsis, localized as an extensive left empyema and a subdiaphragmatic abscess. The amputation stump was heavily infected. There was also marked coronary sclerosis, with occlusion and an infarct of the heart apparently several days old.

Two very striking and unusual cases called my attention to the clinical importance of the high sugar content of the blood and tissues in cases of diabetes with infection. Both these cases have been clinically diagnosed as gas gangrene but repeated cultures, both aërobic and anaërobic, as well as guinea-pig inoculation failed to reveal anything other than colon bacilli.*

* Another odd finding secondary to high sugar content of the blood and tissues was encountered in a diabetic with pulmonary infection due to Aspergillus. (Lichwitz, L., in: Mohr, L. and Staehelin, R., Handbuch der Inneren Medizin, 2 aufl., Berlin, 1926, p. 779.) Large amounts of oxalates were excreted in the urine, and numerous crystals of calcium oxalate were present in the sputum.

Case No. 3747 was a man, aged fifty-eight years, whose diabetes was known to have existed for only a month, although undoubtedly it had been present for some time previously. He had suffered from intense pruritus and through scratching had produced several infected wounds in the inguinal regions. The cause of death was an extensive phlegmonous abscess involving the inguinal region and the left flank. At postmortem, as in examination during life, there was marked crepitation of the tissues but a considerable amount of rather creamy pus together with a definitely purulent condition of the underlying muscles, coupled with repeated cultures negative for Bacillus welchii and positive for Bacillus coli led us to believe that the latter was the offending agent. Cultures and animal inoculations at postmortem also failed to produce any organism other than the colon bacillus. This strain of Bacillus coli was an extremely active gas producer. Unquestionably this organism in the sugar-laden tissues had succeeded in producing the amount of gas that had proved so confusing from the clinical standpoint.

Localized infection, particularly of the internal organs, may give very little warning of its presence until well advanced. Thus, in Case No. 1096 an acute inflamed appendix was removed from a girl, aged eight years, whose diabetes had been present for 2.8 years. She entered the hospital with some pain in the right side and nausea of two days' duration. Her temperature was 99.4° F. There was some tenderness and spasm in the right lower quadrant. In view of these relatively vague symptoms the white cell count was fortunately fairly suggestive, being 31,000. However, high white cell counts are so frequent in coma or in cases verging on coma that that alone is a feeble reed on which to lean. Judging from the appearance of the appendix both in gross and on microscopic examination one would have expected a much longer history and much more severe symptoms. Its distal portion was heavily coated with fibrin and permeated throughout with polymorphonuclear leukocytes. It was dark and gangrenous in color and the lumen was bulging with pus.

Focal infections are of considerable importance in keeping down sugar tolerance, and are as frequent in diabetic as in non-diabetic patients. Teeth, tonsils and gall bladder are all possible points of localized chronic inflammatory processes. Here again the pathology is similar to that of non-diabetics.

SYPHILIS.

While syphilis, particularly in the congenital form, with its tendency to involvement of the liver and pancreas, is a possible etiological factor in the production of diabetes, nevertheless the incidence of demonstrable pathology is very low. I have not seen a pancreas in this series where I felt syphilis could be responsible for the changes present, and even the occurrence of syphilitic lesions in other organs is very rare. Warthin and Wilson[6] emphasize the importance of syphilitic pancreatitis, but my material is apparently very different from theirs. Among 35 fatal cases of syphilis and diabetes reported by Joslin,[7] only 5 deaths were possibly due to syphilis. In 4 cases the cause of death was not known.

In my series 2 deaths only were due to the disease. One case, a colored female, aged fifty years, with diabetes of three years' duration, died of hemorrhage from a syphilitic ulcer of the trachea. The other case, a male, aged forty-two years, died from a ruptured abdominal aneurysm. His diabetes had been present for three months.

TUBERCULOSIS.

Although tuberculosis was formerly responsible for many of the deaths of diabetic patients, only 13 deaths from tuberculosis occurred in this series. Only 10 were due to tuberculosis alone as 2 were complicated by coma and 1 by gangrene. The pancreas was not involved in any of these cases, and only in 2 cases of generalized miliary tuberculosis (both non-diabetic) have I seen pancreatic involvement.

This is in marked contrast to a generation ago, when nearly half the fatal cases of diabetes died from tuberculosis.

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CHAPTER XI.

THE PATHOLOGY OF THE NERVOUS SYSTEM.

Although diabetes mellitus is intimately connected with the nervous system (emotional glycosuria, decreased carbohydrate tolerance during periods of mental anxiety), demonstrable changes in the nervous system are those due to complications of the disease, rather than to diabetes itself.

The most striking changes are those secondary to vascular disease. Cerebral hemorrhage is much less frequent, relative to other types of arteriosclerotic disorders, in diabetics than in non-diabetics. The same holds true for cerebral softening. Among the 300 cases of this series, only 7 were due to cerebral hemorrhage. One of these was complicated by coma. Cerebral softening secondary to thrombosis occurred in 1 case. Sections of the brain in Case No. 4606, dying as a result of massive intraventricular hemorrhage, are shown in Figs. 77 and 78. This case was a woman, aged sixty-seven years, whose diabetes had been present 2.1 years. The hemorrhage was secondary to rupture of the left cerebral artery. Of course, changes of this type are in no sense peculiar to diabetes.

Unfortunately there were relatively few autopsies in this series in which permission for examination of the head was granted.

However, from the brains which I have personally examined, and from the reports in the literature, there are no changes distinctive of diabetes other than the abnormal glycogen deposits in certain cases of diabetic coma. I have not seen the droplets of glycogen described by Geipel as occurring in the pyramidal cells of some cases of diabetic coma. Casamajor[1] has described the presence of droplets of glycogen in the perivascular lymph spaces of the brain in coma cases, although these are frequently present in the infectious diseases as well. When the glycogen is present in large amounts, droplets may be present in the glia cells. I have seen this type of glycogen deposition in 3 diabetic brains, 2 from coma cases. Spielmeyer[2] states that the normal brain is devoid of glycogen.

While neuritis, particularly of the lower extremities, is common in diabetes, but little is known of the underlying lesions. Pares-

thesia and anesthesia are not rare. Apparent trophic disturbances are usually due to a deficient blood supply. Woltman and Wilder[3]

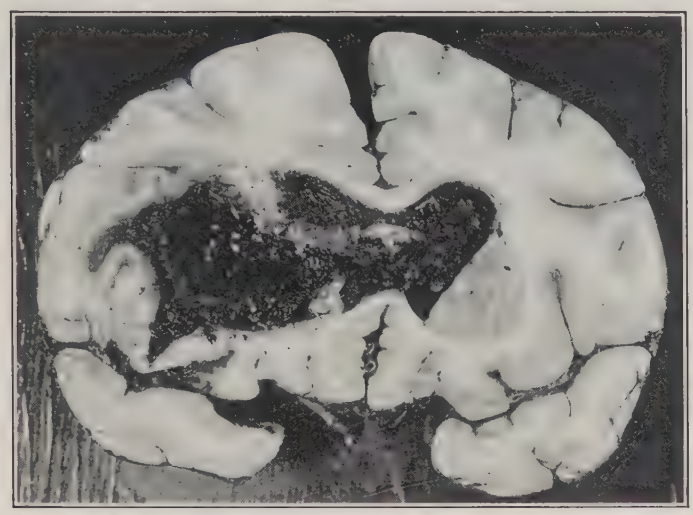

FIG. 77.—Massive intraventricular hemorrhage from middle cerebral artery. No. 4606. Female, aged sixty-seven years. Duration of diabetes 2.1 years.

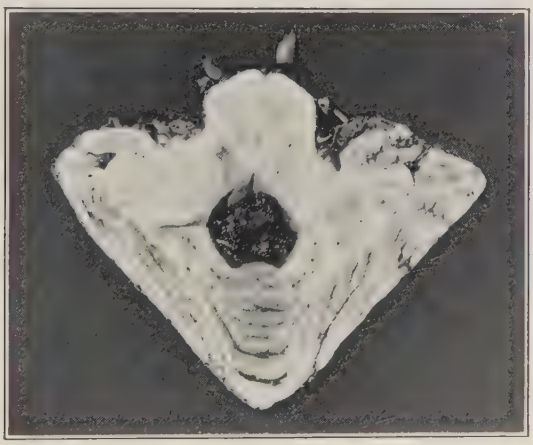

FIG. 78.—Hemorrhage in fourth ventricle from same case as above.

have collected 38 cases from the literature and have reported 10 additional cases. In 3 of these the spinal cords were examined and

showed only slight lesions, most easily explained on an arteriosclerotic basis, rather than similar to the degenerative changes of pernicious anemia. The posterior columns were the most involved.

Woltman and Wilder[3] describe in the peripheral nerves degeneration associated with marked sclerosis of the intraneural vessels, and emphasize that arteriosclerosis is the most important factor in the lesions of nerves in diabetics.

In the relatively few specimens of peripheral nerves I have examined, I have failed to note any significant changes. None of the specimens came from patients with clinical evidence of neuritis.

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CHAPTER XII.

THE PATHOLOGY OF DIABETES IN CHILDREN.

In children alone may we hope to find pure diabetic lesions uncomplicated by any of the degenerative processes of age. Any changes which we find in the pancreas in children, it is fairly safe to say, are definitely associated with the diabetic process. For this reason it is discouraging, at least from the standpoint of pathology, that many of the pancreases in diabetic children fail to show any definite pathological change. However, this is of great importance as regards prognosis.

Of the 22 fatal cases reported in Table 37, but 4 had been treated with insulin for any length of time. A few of the others received insulin when, already in terminal coma, they were first seen by a physician. Of the 4 cases treated for any length of time with insulin, 1 was killed by an automobile, 2 were treated in the dawn of insulin therapy and 1, a negro girl, was treated for six months before death from coma, precipitated by a severe sore throat, the duration of the diabetes being four years so far as known.

What a tribute to insulin—and what striking proof that diabetes is due to insulin deficiency!

The cause of death in the diabetes of childhood is coma. In 5 cases coma was accompanied by infection sufficiently severe to be recognized at postmortem.

From this one may draw the conclusion that while under insulin treatment patients do not die of diabetes primarily but from complications of diabetes.

While the pancreas is noted as small in many cases, this observation is uncertain. The size of the pancreas is far from constant even in normal persons, and the temptation is constant to regard as significant an organ slightly smaller than normal, paying no attention to those in the series that may slightly exceed normal.

In light of the experimental evidence relative to the removal of portions of the pancreas, it is obvious that the pancreas must be very small indeed before the deficiency is of any significance, provided, of course, that there is a normal amount of insular tissue in proportion to the acinar tissue.

TABLE 37.—CASES OF DIABETES UNDER FIFTEEN YEARS OF AGE AT ONSET.

Case No.	Sex.	Age at death, yrs.	Duration.	Cause of death.	Islands of Langerhans.	Arterio-sclerosis.
3178	♀	1.5	3–4 mos.	Coma	.....	—
A26-27	♂	2	1 mo.	Coma	Lymphocytic infiltration; hydropic degeneration	—
Jos. 865	♂	2.2	17 das.	Coma	.....	—
A22-3	♂	2.9	?	Coma; broncho-pneumonia	Hydropic degeneration; pyknotic nuclei	—
Jos. 2849	♂	3.8	1.1 yrs.	Coma; otitis media	Pyknotic nuclei	—
A27-100	♂	4	2 wks.	Coma	Lymphocytic infiltration; H+	—
Jos. 272	♀	5.8	1.9 yrs.	Coma; broncho-pneumonia	Few	—
A11-23	♀	6	6 wks.	Coma	Few	—
John	♂	6	1.3 yrs.	Accident; fractured skull	Hypertrophy ("cobra" type)	—
Starrow	♀	6	6 wks.	Coma	Lymphocytic infiltration; hydropic degeneration	—
3545	♀	12	?	Septicemia	.....	—
Stansfield	♀	12	5 das.	Coma	Lymphocytic infiltration	—
9949	♀	12	4 yrs.	Coma; sore throat	.....	+
A21-103	♂	12	1.8 yrs.	Coma; acute pericarditis	.....	+
A15-68	♂	13	11 mos.?	Coma	Few; hydropic degeneration	—
A22-23	♂	14	1 wk.	Coma	Slight fibrosis	+
M904	♂	15	1.6 yrs.	Coma	Lymphocytic infiltration	—
A22-141	♀	15	1 mo.	Coma	Few	—
3125	♀	15	8 mos.	Coma	.....	—
U23-10	♂	15.3	8 "	Coma	Few	—
M978	♂	16	5.5 yrs.	Coma	Slight fibrosis	+
H15-102	♀	38	29 "	Coma	Slight fibrosis; ? hydropic degeneration	+

Quantitative studies of the amount of insular material present in the human pancreas are not yet practicable. The difficulties in the way of enumerating the islands of the pancreas are tremendous and in none of this series has it been attempted. However, from a number of sections it is possible to gain some idea of the various numbers of islands present in different portions by the rough comparison of those encountered in usual routine microscopic sections. On this basis, 5 cases showed an apparent decrease in the normal number of islands. If lack of pancreatic tissue were of primary importance we should have congenital cases of diabetes rather than cases developing in childhood.

Perhaps the one most characteristic lesion of the islands in diabetic children is lymphocytic infiltration, as I have already emphasized.[1] This lymphocytic infiltration, present in 5 cases, rarely occurs in older individuals. It strongly suggests the action of some toxic substance or possibly a mild reaction to the necrosis of island cells produced through functional overstrain. The short duration of these cases is very suggestive, in 4 being six weeks or less and in 1 case of any considerable duration being only nineteen months. Lymphocytic infiltration is obviously not a primary lesion of the islands but rather a response to preëxisting injury.

Hydropic degeneration was positively diagnosed in 4 cases and suspected in 1.

The islands were entirely normal from the qualitative standpoint in 8 cases, and normal both in number and histology in 4.

A fairly typical case is M904, a boy, aged fifteen years, whose diabetes had begun 1.6 years before death in coma. This was a pre-insulin case. The pancreas was small. The islands showed marked lymphocytic infiltration, but their number was normal. There was no involvement of the acinar tissue. The heart was negative. There was marked glycogenic infiltration of the epithelium of Henle's loops and also of the liver-cell nuclei.

The fact that hyaline degeneration, fibrosis and other irreversible tissue changes aside from lymphocytic infiltration are extremely rare is of great importance from the practical standpoint. One case of slight hyaline change was found in this group. Whatever it is that produces insulin deficiency in children is not inexorably progressive. In other words, the outlook for the child diabetic is not one of a steady downhill course, but rather one where there is considerable hope that through satisfactory treatment the progress of the disease may be held in check. This is further substantiated by clinical observations.

Most important of all, in children the regenerative powers of the pancreas should be at their height. There is more opportunity for the organs in a child to stage a comeback than there is in an adult.

One case in this series, which I have been permitted to study through the kindness of Dr. Henry J. John, showed several hypertrophic islands of the columnar or "cobra" type. This boy, whose diabetes was of 1.3 years' duration, was doing very well under insulin treatment when killed by an automobile.

Perhaps the best evidence of regeneration is presented by Boyd,[2] who reported the case of a boy, aged nine years. When two years

of age diabetes was recognized, and by dietary treatment the diabetes was kept under control with the exception of lowering of tolerance due to repeated attacks of dysentery. There was very little growth and the general condition became steadily worse. December, 1922, insulin treatment was begun and during the year the insulin requirement was reduced from 90 to 30 units. There was a commensurate improvement in the general condition. Death was due to fracture of the skull accidentally sustained. At autopsy the pancreas was normal with the exception of scattered pyknotic nuclei in some of the island cells. Boyd emphasized the presence of very large numbers of island areas at the periphery of the pancreas, sometimes twelve or fourteen in a low-power field. They were often small, not more than six or eight cells occurring in a section, and their association with the terminal ducts and central acinar cells was readily observed. In these islands α cells were almost entirely absent.

In the discussion of this paper Bensley stated that he had little doubt that some small bulbous islands adjacent to a duct and strongly resembling the islands produced in experimental animals by regeneration were newly produced islands.

While diabetes in children is usually severe, it becomes less severe with the passage of time, and there was 1 case in this series of which the duration was twenty-nine years, without the aid of insulin.

Allan and Wilder,[3] in a study of 17 cases of diabetes in children which resulted fatally, emphasize the potential severity of juvenile diabetes. Two deaths were due to intercurrent disease and 1 was moribund when treatment was started—the others were due to inadequate treatment. Unfortunately no autopsies were obtained.

Arteriosclerosis, while infrequently present, is the only complication other than infection, and, of course, in the children is not sufficiently advanced to produce effects detectable clinically. However, 4 cases, ranging from twelve to sixteen years of age at death, did show evidence of arteriosclerosis, and, of course, this was present in the 1 case of long duration, although the patient was but thirty-eight years of age when she died.

In view of the evidence of hyperpituitarism presented by some diabetic children, the work of Moehlig[4] is of interest. Rabbits placed on a high-fat diet and injected daily with 1 cc. of extract of the posterior lobe of the pituitary gland showed intense arteriosclerosis of the aorta and coronary arteries. These changes were

less apparent on either high-fat diet alone or injections of pituitary extract alone.

I am indebted to Dr. R. H. Major for the protocol of an autopsied case of status lymphaticus occurring in a diabetic girl eighteen years of age. Her diabetes was of three months' duration. The thymus weighed 30 grams; there was general enlargement of the lymph nodes, and hyperplasia of the aorta. The pancreas showed acute and chronic inflammation. The immediate cause of death was apparently sepsis from a furuncle of the right buttock.

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CHAPTER XIII.

THE PATHOLOGY OF DIABETES IN CASES OF LONG DURATION.

Of no little interest are those cases of diabetes which have successfully resisted the disease for a number of years. In this series of 300 cases of diabetes which came to postmortem examination, 23, or 8 per cent, were of fifteen years' duration or longer. In addition, there were 19 cases with ten to fifteen years to their credit, and there were 49 of unknown duration, a few of which presumably had had their diabetes for a considerable period.

There are two factors to be considered in these cases. (1) The long duration of diabetes has given full range for the development of pathological lesions secondary to it; and (2) there has been ample opportunity for the degenerative processes of age to complicate the diabetic portion of the picture.

The case of longest duration in this series is No. 511, a male, aged seventy years, whose diabetes had developed 39.2 years before death. The immediate cause of death was an acute pleuritis accompanied by vague respiratory symptoms. He was well nourished and well developed. The pancreas weighed 50 grams. The islands were normal in number and showed moderate hyaline change and slight fibrosis. There was marked fatty infiltration of the acinar tissue and marked interlobular and interacinar fibrosis with scattered small retention cysts associated with the ducts. The heart weighed 500 grams, the hypertrophy being chiefly of the left ventricle. There was a healed infarct of the left ventricle and marked chronic vascular myocarditis. The coronary arteries were tortuous, showed numerous atheromatous plaques and were markedly calcified. The liver was essentially negative. There was a large cholesterol stone in the gall bladder. The kidneys were of moderate size and both showed a moderate degree of chronic progressive nephritis with some sclerosis of the larger vessels. The aorta showed extreme atheromatous degeneration with marked calcification. There was no gangrene. In other words, in this case the diabetic lesions seen were relatively inconspicuous as compared with the lesions which we may be justified in considering as secondary to arteriosclerosis.

Another case, of 33.7 years' duration, a woman, aged eighty-four years, died from coronary thrombosis. She weighed 138 pounds after one leg had been amputated at mid-thigh. The pancreas weighed only 40 grams. The islands were normal in number and showed a moderate degree of fibrosis. There was a moderate degree of interacinar fibrosis as well. The heart was moderately enlarged, weighing 340 grams, and showed marked chronic vascular myocarditis as well as a healed infarct. No fresh infarct had developed from the thrombosis owing to an insufficient lapse of time. The coronaries were markedly atheromatous and calcified and the left was thrombosed. The liver, weighing 1600 grams, was negative. The kidneys were slightly contracted and showed a moderate degree of chronic progressive nephritis. The aorta showed marked atheromatous change with calcification. The left leg had been amputated for gangrene. There were many gall stones of the cholesterol type, accompanied by a moderate degree of chronic cholecystitis. The eyes showed bilateral cataracts. In this case, just as in the other, while the pancreas showed clear-cut pathology, a considerable number of apparently normal islands were present.

TABLE 38.—CASES OF DIABETES OF FIFTEEN YEARS' DURATION OR MORE.

No.	Age.	Duration.	Cause of death.	Islands.	Aorta, arteriosclerosis.	Gangrene.	Cardiac infarct.	Gall stones.
1595 . .	56	15.0	M	−	+++	−	...	−
3361 . .	54	15.0	M	−	M	−	...	−
889 . .	66	15.3	Infarcts of heart	S+++	+++	+	Fresh; healed	+
DA27-4	76	15.5	Bronchopneumonia	S+	+++	−	...	−
1855 . .	60	16.0?	M	−	+	−	...	−
U22-3 .	53	16.9	Coronary thrombosis	H+++	+++	−	Thrombosis; healed	+
5513 . .	73	16.9	Gangrene	S+	+++	+	...	+
U23-8 .	59	17.3	Phthisis	S+++	+	−	...	−
6778 . .	67	20.7	Infarct of heart	H++; S++	+++	−	Fresh; healed	−
1207 . .	70	21.8	Myocarditis	S+; H++	+++	−	...	+
66 . .	72	22.2	Cardiac decompensation	? hydropic degeneration; small	+++	+	...	−
1020 . .	50	23.2	Carbuncle septicemia	H+++	++	+	...	−
U23-13 .	62	25.0	Coronary thrombosis	Few	++	+	Healed	−
M988 .	52	25.0	Septicemia	H+++	M	−	...	−
7104 .	68	25.5	Streptococcus sepsis	H++	+++	+	Fresh	+
DA27-57	54	25.9	Cerebral hemorrhage	H++	+++	−	Fresh; healed	−
1603 . .	63	28.1	Chronic myocarditis	Hypertrophy	+++	−	Healed	−
H15-102	38	29.0	Coma	Hydropic degeneration, S+	M	M	...	M
4996 . .	76	29.4	Infarct of heart	Few; H+	+++	+	Fresh, with rupture	+
M886 .	54	30.2	Gangrene and septicemia	H++	M	+	M	−
6365 . .	84	33.7	Coronary thrombosis	S++	+++	+	Thrombosis; healed	+
3804 . .	66	35.1	Pulmonary embolism	Hypertrophy	+++	−	...	−
511 . .	70	39.2	Acute pleuritis	H++; S+	+++	−	...	+

H = hyalimization. S = fibrosis. M = information missing.

It speaks well for the treatment of the present day that several of these cases have outlived their normal expectancies of life from the age at which they had first developed diabetes.

The marked degree of arteriosclerosis in all these cases of long duration is peculiarly striking. All but 4 showed severe arteriosclerosis of the aorta, considerably more than would be ordinarily expected in persons of their ages. No case was devoid of arteriosclerosis.

Infarcts of the heart were present in 9 cases and 2 cases showed thrombosis of the left coronary artery in addition. Two of the cases showed fresh infarcts alone, and rupture had occurred through 1. Of the 7 cases with healed infarcts, 3 showed fresh also. The proportion of infarcts is almost incredibly high in this small series of cases, amounting to 39.1 per cent.

Gangrene occurred in 9 cases, or 39.1 per cent.

The causes of death in these cases differ strikingly from those of Naunyn,[1] over half of whose cases died of coma or tuberculosis.

The occurrence of definite pancreatic lesions in these mild cases of long duration, and the relative absence of these lesions in the severe cases of short duration in the children, is just the reverse of what might be expected in attempting to correlate pathology and symptomatology. A glance at Table 38 shows that all but 7 cases showed some degree of hyalinization or fibrosis of the islands. Two showed evidences of hypertrophy of the islands, 1 showed few islands, and 1 showed small islands with probable hydropic degeneration.

It is noteworthy that in this series of 23 cases, all but 1 of which was over fifty years of age, there was not a single case of malignant disease.

Reference.

1. Naunyn, B.: Der Diabetes Mellitus, Wien, 1906, p. 478.

CHAPTER XIV.

HEMOCHROMATOSIS.

The association between diabetes and hemochromatosis has long been known. In fact, one of the names applied to this latter lesion is "bronze diabetes." While hemochromatosis is primarily a lesion involving the liver, nevertheless other parenchymatous organs are

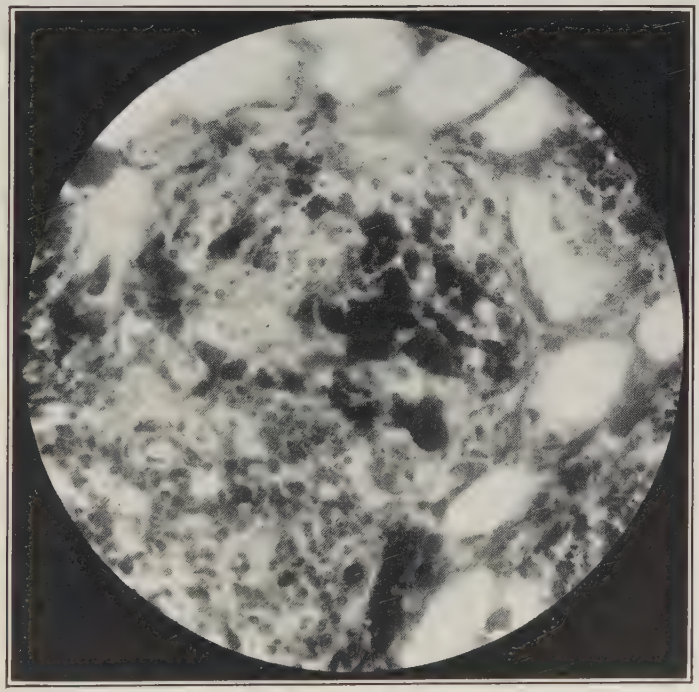

Fig. 79.—Hemochromatosis. Island partly destroyed by deposition of pigment.

involved as well. The liver may be regarded as the primary reservoir for the deposit of the abnormal pigment that characterizes the disease. When this primary depot or reservoir is partially filled the pigment overflows into other organs. Usually the pancreas is

one of the first to receive the overflow, followed closely by the skin, the adrenals, the lymph nodes and the heart. The kidneys rarely, if ever, attain a very marked pathological pigmentation owing to the fact that most of the pigment is deposited in the epithelium of the kidney tubules, and hence as soon as the cells are involved to the extent that they become necrotic they are desquamated and pass out with the urine. One of the means of diagnosis of the disease is the finding of iron-containing epithelial cells in the urine.

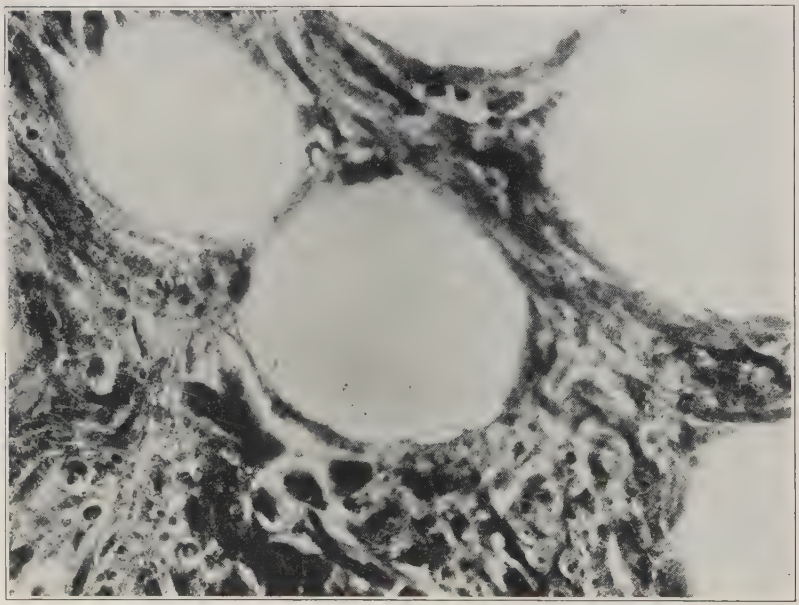

FIG. 80.—Hemochromatosis. Pancreatic parenchyma almost entirely replaced by heavily pigmented fibroblasts and wandering cells.

The initial step in the genesis of hemochromatosis, the formation of the pigment, is as yet not clear. Nevertheless the effect of the pigment and the correlation of the lesion with the clinical course of the disease are very thoroughly known. In other words, we have in cases of hemochromatosis with diabetic symptoms practically an experimental diabetes, that is to say, a diabetic condition produced by the action on the pancreas of a known substance. Hemochromatosis without severe involvement of the pancreas does not cause diabetes mellitus. In cases where there is severe pancreatic involvement diabetes does appear and is identical with the diabetes of

so-called idiopathic origin. "If the pathology referable to the pigment sclerosis of other organs is disregarded this diabetes differs in no way from diabetes mellitus except that the course is more rapid. Here then we have an ideal means of studying diabetes with a known etiology and a fairly rapid course."*

"Bronze diabetes" was first described clearly by Hanot.[1] The bronzing of the skin is, of course, not a necessary concomitant of the diabetic syndrome, for it largely depends on how much of the iron has been deposited in the skin. There is not only deposition of iron in the skin, but there is as well an increase of the melanin in the skin causing still further pigmentation. This last is secondary to severe involvement of the adrenals.

Hanot[1] felt that the diabetes was the underlying factor in the condition. However, Opie[2] pointed out that the "bronze diabetes" of Hanot is identical with the hemochromatosis of von Recklinghausen.[3] Two pigments are involved, the one in which iron can be demonstrated, hemosiderin; and the other in which iron cannot be demonstrated and is presumably held in masked form, hemofuscin; both are derived from the breakdown products of hemoglobin. Mallory[4] believes that hemosiderin is the product of the intracellular digestion of hemofuscin and that both are derived from the blood pigment.

It is only in the most advanced cases, as a rule, that hemochromatosis produces diabetes. Usually death occurs from hepatic insufficiency before this event or the patient dies from some intercurrent infection. Of 10 cases of hemochromatosis autopsied in Mallory's laboratory none showed sugar in the urine, although they were well-developed cases of the disease. The frequent association of exposure to copper with these cases led Mallory to believe that it might be an etiological factor and animal-feeding experiments enabled him to produce through the administration of small amounts of copper over a long period of time lesions very similar to those of hemochromatosis. This observation that copper might be an etiological factor was confirmed by Hall and Butt.[5]

At present the etiology must be still regarded as *sub judice*. However, this uncertainty as to the primary etiology in no way interferes with the value of hemochromatosis in throwing light on the pathogenesis of diabetes. In the first place, it is of great importance in showing that perfectly typical diabetes can be produced by a definitely known clinical entity which is known not to

* Quoted from Warren, S.: Am. Jour. Path., 1925, **1**, 415.

be an effect of the diabetic process but to produce it. Moreover, the development of the diabetes is apparently directly related to the extent of its involvement of the islands of Langerhans.

Thus Case U23-31 died of cirrhosis of the liver with ascites, a perfectly typical case of hemochromatosis. There was no diabetes, and while there was a moderate amount of pigmentation of the pancreas, nevertheless, as can be seen from Fig. 81, there is practically no involvement of the islands, many normal islands being

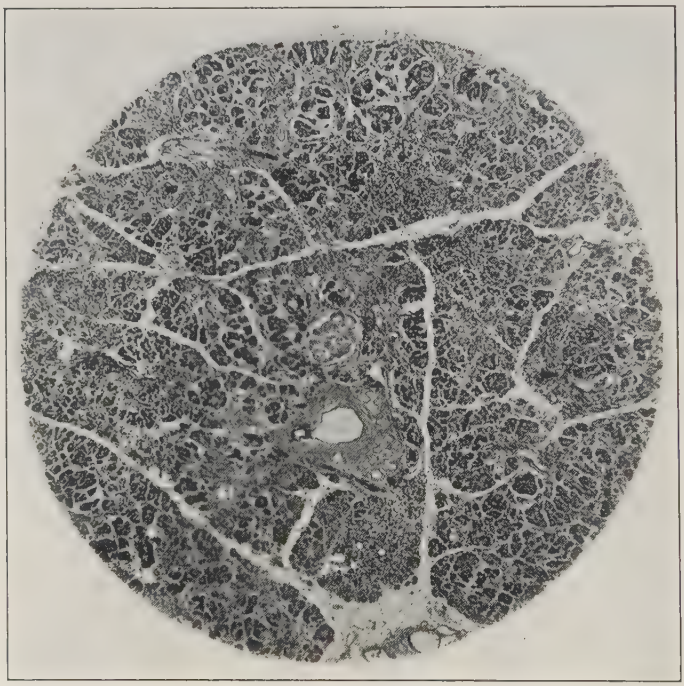

FIG. 81.—Hemochromatosis. Moderate pigmentation of pancreas. Note interacinar fibrosis, also practically normal island in center.

seen scattered throughout the section. In contrast to this are Fig. 79 and Fig. 80, both from a case of hemochromatosis with heavy pancreatic involvement and with the development of diabetes.

Of the 259 pancreases examined in this series, 3 showed marked changes characteristic of hemochromatosis and gave the clinical symptoms of diabetes. In addition, 1 case still alive and in fairly good clinical condition was proved, by excision of the skin and the finding of iron pigment in it, to be definite hemochromatosis.

Case A22-115, from the Peter Bent Brigham Hospital, was that

of a male, aged forty-one years, whose diabetes was known to have existed at least three months and presumably somewhat longer. He was obese and showed general anasarca. The pancreas weighed 90 grams. In gross, it was chocolate-brown in color, and microscopic examination showed considerable amount of deposition of hemofuscin and hemosiderin in the islands and acinar cells with a good deal of fibrosis. Many of the islands were very severely damaged. The liver was markedly cirrhotic and pigmented.

The heart weighed 310 grams and was markedly pigmented. An analysis of the organs for copper yielded 3.35 mg. from 952 gm. of parenchymatous organs. This man had worked for a considerable period of time milling and turning brass and copper. In this pancreas, as in almost all, although there were many severely damaged islands, there were a very few which showed no definite involvement.

Another case, that of a man, aged fifty-six years, was of interest owing to his tremendous insulin resistance, and will be described in detail in Chapter XV.

A third case studied was incomplete, that of a male, aged fifty-three years, dying of diabetic coma with hemochromatosis. The pancreas was somewhat increased in size, dark brown in color. There was marked pigmentation of the islands with much fibrosis. There was moderate pigmentation and a moderate degree of interacinar and interlobular fibrosis of the acinar tissue. The heart weighed 297 grams and was negative except for a very slight amount of pigmentation. The aorta showed a moderate degree of arteriosclerosis. The known duration of diabetic symptoms was five weeks.

In 1 case of hemochromatosis I was able to examine the pituitary gland, and found there a moderate amount of pigmentation. This case showed no diabetes.

It must be emphasized that the deposition of pigment in the pancreas in hemochromatosis is by no means selective for the islands, but involves the acinar tissue as well. In other words, it is not a specific but a generalized process, and the evidence of pancreatic involvement is only of value from the standpoint of the relation of the diabetes to the pancreas rather than evidence in favor of the insular hypothesis itself.

Whatever cell is involved, the mechanism is practically the same. First, hemofuscin appears, then hemosiderin. Finally, the amount of pigment is sufficient to prevent life of the cell. When necrosis occurs, some of the pigment is taken up by wandering cells, some

by the stromal cells. The stroma condenses, new parenchymatous cells are formed and new stroma is laid down, only for the process to repeat itself.

As Root and I[6] have already mentioned, in hemochromatosis frequent evidences of attempts at regeneration can be seen, considerable numbers of mitotic figures being found in the island cells.

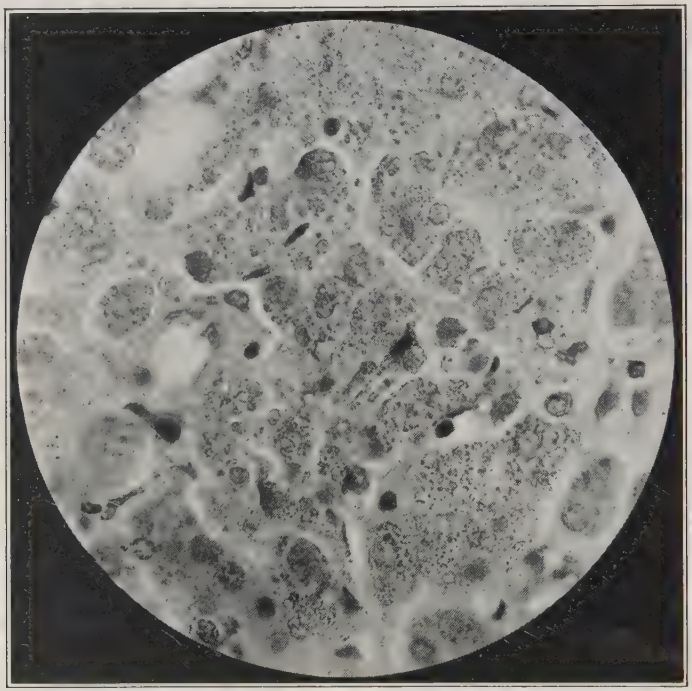

FIG. 82.—Hemochromatosis. Early pigment deposition in island of Langerhans. No. A17-8. Adult male. Diabetes had not developed in this case, owing to the presence of many pigment-free islands.

Case A17-08, a non-diabetic from Dr. Mallory's laboratory, is of particular interest in that there were a considerable number of pigment-free as well as pigmented islands and in the former islands mitotic figures could occasionally be found.

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CHAPTER XV.

THE PATHOLOGY OF INSULIN-RESISTANT CASES.

From the theoretical standpoint insulin-resistant cases are of great interest, though their rarity makes their practical importance slight. According to Root,[1] a case cannot be considered as falling in this group unless 200 or more units of insulin are needed per day.

I have seen only 1 case, which is described in some detail by Root.[1] I am indebted to Dr. George Rukstinat for the autopsy protocol and for an opportunity to study the tissues microscopically. This case, Joslin's No. 6247, a male, aged fifty-two years, in 1923 was found to have a cirrhotic liver and no evidence of diabetes. In October, 1926, diabetes developed. In August, 1927, on a diet of carbohydrate, 78 grams; protein, 60 grams, and fat, 123 grams, he excreted 40 to 90 grams of glucose in the urine daily and diacetic acid was present, although he was receiving 100 units of insulin daily. In September, 1927, he went into coma and required 525 units daily. Insulin was gradually increased until October 22, when he was receiving 840 units per day. October 27, he was given 1600 units and died in coma October 30, 1927, although he had received 1680 units of insulin in the previous twenty-four hours.

The essential findings in the postmortem were a finely granular dark liver, and the pancreas showed marked fibrosis and lipomatosis. Microscopic examination revealed deposits of hemofuscin and hemosiderin in the great majority of the organs and very large amounts in the liver and in the pancreas. There was very little pancreatic tissue present, most of it being replaced by fat and fibrous tissue. While all of the epithelial elements of the pancreas were pigmented there were a very few islands which were nearly normal. In the adrenals the cells of the zona glomerulosa were extremely heavily infiltrated with the pigments. Presumably but a very slight amount of functioning insular tissue was present in the pancreas, and the liver was very severely damaged. There was sufficient liver damage to explain a very considerable degree of interference of the glycogen with the glycogen-storing function.

This undoubtedly is one explanation of the extremely high insulin requirement.

Allan and Constam[2] have reported a case of hemochromatosis with severe diabetes, in which several hundred units of insulin were needed daily, once 1000 units being given. In this case, just as in the preceding, the daily insulin requirement is greater than the theoretical insulin output of the normal pancreas (about 300 units), and presumably some other mechanism, in addition to insulin deficiency, must be involved. The severe liver damage is in all probability a very important factor.

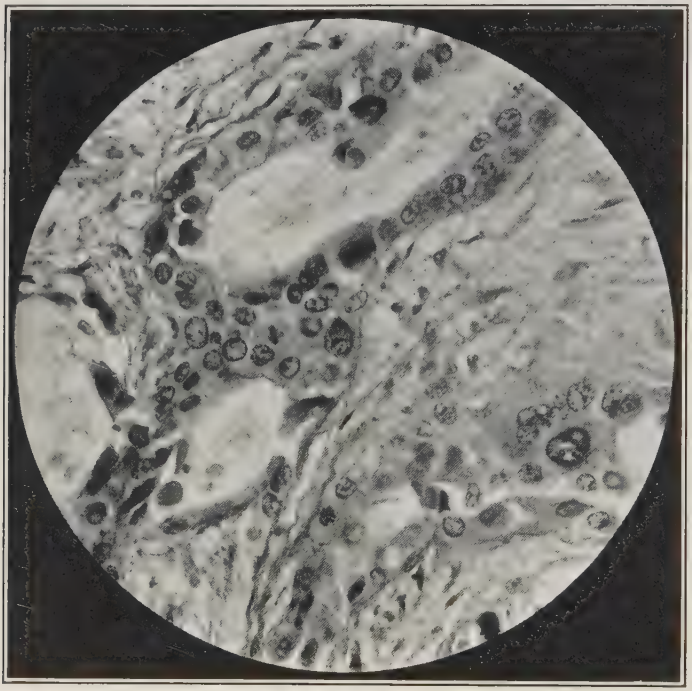

FIG. 83.—Carcinoma of pancreas. Very large insulin requirement. No. U24-33. Female, aged sixty-nine years. Duration of diabetes sixteen years. Phosphotungstic acid hematoxylin stain. × 280.

Another case, while it falls short of the true insulin-resistant type, is nevertheless very instructive. U24-33, a diabetic woman, aged sixty-nine years, had been a relatively mild case for about ten years. A few months before death there was a marked increase in insulin requirement, 50 to 100 units per day being necessary.

At autopsy a large carcinoma of the pancreas was found which had destroyed the bulk of the gland. The last 3 cm. of the tail was uninvolved, and most of the acinar tissue there had atrophied due to duct obstruction, while the remaining islands had hypertrophied. Although these islands must have been under considerable functional strain, they showed no evidence of hydropic degeneration.

Renal glycosuria[3] is always insulin-resistant, as would be expected. However, insulin does lower the blood sugar in these cases.

Diabetes associated with other endocrine disturbances may be insulin-resistant. Pituitary disease[4,5] is particularly prominent in this group, the hyperpituitarism apparently affecting the carbohydrate function directly or through the nervous system rather than through any effect on the pancreas or adrenal.

Root[1] notes that cases with skin lesions may be insulin-resistant, and suggests that there may be both an allergic factor and a problem of carbohydrate storage. However, biopsy specimens of skin from non-diabetic persons, that I have been able to examine through the courtesy of Dr. A. M. Greenwood, show but little variation in glycogen content between normal skin and skin with various pathological conditions.

Liver injury[6,7] is one of the most important causes of this phenomenon. While liver insufficiency does not in itself produce diabetes, it does profoundly influence a coëxistent diabetes. The importance of the liver for the prompt removal of sugar from the blood is well known, and obviously any marked interference with liver function would lead to lessened glycogen storage and so decrease the effectiveness of insulin in lowering blood sugar. In certain of the non-diabetic cases of cardiac decompensation with liver damage and of cirrhosis of the liver, I have found a less amount of intracellular glycogen than that usually encountered.

In marked contrast is a case of portal cirrhosis cited by Bordley.[8] A male, aged forty-nine years, was a severe diabetic for five years, and then developed jaundice followed by cirrhosis in April, 1927. In December, 1927, the diabetic symptoms disappeared, and in April, 1928, and in 1930 showed no evidence of diabetes mellitus.

So little is known pathologically of other types of insulin resistance that discussion of them would be of little value. An excellent summary of their clinical aspect is given by Root.[1]

The outstanding feature of insulin-resistant cases is that even complete failure of insulin production by the patient cannot explain them. While the insulin requirement of a depancreatized man is

unknown, if we may take the requirement per kilo of a depancreatized dog as a basis, it should be about 300 units of insulin per day. Thus a patient requiring 1000 or more units per day must have some other difficulty than simple insulin deficiency. This in most cases is lack of capacity for carbohydrate storage, usually through liver injury or atrophic muscles.

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CHAPTER XVI.

HYPERINSULINISM AND PATHOLOGICAL EFFECTS OF INSULIN ADMINISTRATION.

The case which gave the final proof to the insulin origin of diabetes, that of Wilder, Allan, Power and Robertson[1] also laid the foundation for a new clinical entity, hyperinsulinism, the basic physiological pathology of which is hypoglycemia. This case is of sufficient importance to warrant presenting a brief summary of it.

The case was that of a man, aged forty years, who had had a gastro-enterostomy in 1919 and renal colic in 1924. In January, 1925, the fasting blood sugar was normal, one specimen of the urine was sugar-free while others showed traces of sugar. October, 1926 the patient came to the Mayo Clinic, complaining of attacks of faintness and weakness for the past eighteen months. These were accompanied by profuse perspiration and trembling. They usually came on when meals were delayed or if unusual exertion was undertaken. The patient found that they could be prevented by eating between meals. The first attack resulting in collapse was in November, 1925. The similarity of it to an insulin reaction led to the diagnosis of spontaneous hyperinsulinism. Exploratory operation was performed, December 4; the pancreas found to be large, hard and nodular, and nodules were present in the right lobe of the liver. The diagnosis of carcinoma of the islands of Langerhans with metastasis to the liver was made. January 3, 1927, death occurred, apparently from exhaustion. The liver was much enlarged, weighing 3392 grams. There were five nodules in the liver, ranging from 5 to 0.3 cm. in diameter. The pancreas weighed 120 grams. The tail was thickened and enlarged, and scattered through it were yellowish-gray rounded nodules ranging from 1.3 cm. in diameter downward. In addition, there was a small cyst at the extreme tail of the pancreas. Microscopic examination showed the cells to be characteristic of those of the islands, as were the nodules in the liver. There was a very large amount of glycogen in the liver cells and in the convoluted tubules of the kidney.

Analysis of the liver showed it to contain 8.25 per cent glycogen. Assay of the insulin content of the liver tissue showed that there were approximately 40 units of insulin for each 100 grams of tumor tissue. It is peculiarly interesting that there were large amounts of glycogen in the epithelium of the convoluted tubules of the kidneys in this case of hyperinsulinism, while in the diabetic cases who are deficient in insulin glycogen frequently is deposited here; with the administration of insulin the glycogen deposit disappears and the kidney resembles that of the normal individual.

Closely following this case were the cases of Thalhimer and Murphy,[2] in which a large nodule of cells resembling those of the islands was found in the pancreas, apparently a low-grade carcinoma; and of McClenahan and Norris,[3] in which a large adenoma of island-cell type had given rise to hypoglycemic symptoms.

Perhaps the most interesting of the recently reported cases of hyperinsulinism is that by Howland.[4] A married woman, in September, 1922, became semiconscious and restless with sweating and vomiting. At the end of an hour she felt fairly well again. Six of these attacks occurred up to 1924, when they became more frequent and lasted longer, occasionally for twelve hours. Later on she discovered that a glass of milk drunk at the first sign of an attack might ward it off. The physical findings were essentially negative. The blood sugar during one attack dropped to 0.04 per cent. This attack was promptly relieved by the administration of intravenous glucose. March 15, 1925, operation was performed and an encapsulated nodule 1.5 cm. in diameter, fairly well demarcated, found in the middle of the pancreas. On microscopic examination the tumor was diagnosed as a carcinoma of the island of Langerhans, owing to the resemblance of the cells to the island type and the presence of scattered mitotic figures. In places the tumor cells directly invaded the surrounding pancreatic tissue. The postoperative course was uneventful and there has been no recurrence of attacks since operation. No evidence of metastasis was noted at the time of operation.*

That overproduction of insulin may be present with an apparently normal pancreas has been shown by the case of Finney[5] and Case 2 of Allan.[6] Unfortunately the resected portions of the pancreas showed no distinctive pathology.

* A somewhat similar case has just been operated on by Dr. Francis C. Newton of the Peter Bent Brigham Hospital, and an adenoma of island-cell type removed.

PATHOLOGICAL EFFECTS OF INSULIN ADMINISTRATION.

An abundant literature[7] has grown up which deals thoroughly with the so-called insulin reaction or hypoglycemia. A wide range of symptoms has been reported, even to transient attacks of hemiplegia.[8] Little, however, is known as to the demonstrable anatomical changes.

Wohlwill[9] has described 2 fatal cases in which the brain was examined after death. The first was a woman, aged sixty-two years, whose diabetes had been present two years. A breast abscess developed. For three days before death, which occurred in coma, she had received 100 units of insulin daily. Her urine was sugar-free and there was no acidosis.

The second case, a diabetic, aged twenty-nine years, whose disease was of one and one-quarter years' duration, was admitted in coma. Insulin to the amount of 135 units was given the first day, 70 units the second and 90 the third, when death occurred. The blood sugar dropped from 0.462 to 0.065 per cent in twenty-four hours.

Sections of the brain in each case showed a marked amœboid appearance of the glia cells. The ganglion cells showed degenerative changes, with pyknotic nuclei and loss of normal staining reaction, and in the first case the axis cylinders were markedly swollen and irregular.

Through the courtesy of Dr. R. H. Jaffé, I have been able to examine the kidneys from a case of insulin nephrosis. The patient was a woman, aged thirty-seven years, whose diabetes was of unknown origin. Postmortem examination showed bronchopneumonia, a somewhat fibrosed pancreas with moderate hyalinization of the islands, a slight rheumatic endocarditis of the mitral valve and the changes in the kidneys. The right kidney weighed 290 grams and the left 285 grams. They were edematous; the capsule stripped readily from a smooth, light-brown surface. On cut section the tissue bulged above the capsule. The cortex measured 8 mm. in thickness and was hyperemic; the pyramids, while poorly defined, were pinkish-purple in color. Microscopic examination showed marked edema of the interstitial tissue; foamy albuminous material in the lumen of the tubules, which were widely dilated and lined by low cuboidal epithelium; a few sclerosed glomeruli and a moderate degree of arteriosclerosis. A slight amount of glycogen was present in the epithelium of Henle's loops.

However, tremendous amounts of insulin may be given without apparent ill-effect in certain cases. The most striking example with which I am familiar is Joslin's Case No. 6247, reported by Root,[10] in which 1680 units daily failed to prevent the development of coma, and no changes referable to the insulin were found postmortem.

Occasionally local changes are noted in the skin at the site of insulin injections. In the first few months of insulin production painful nodules were rarely noted in the skin of injected patients, developing soon after injection and persisting for some weeks. These were apparently due to the type of antiseptic then in use, and are never seen at present.

Localized atrophy of the subcutaneous fat is due to repeated injections of insulin in the same area. Barborka[11] and Depisch[12] have reported several cases. The depressed character of the lesions, which range from 2 to 9 cm. in diameter and are about 1 cm. in depth, and the absence of any evidence of inflammation, make their appearance very characteristic. Occasionally these foci may be painful. Joslin[13] has seen 3 cases of the latter type. Isaac[14] suggests a small amount of lipolytic ferment may be mixed with the insulin in such instances.

Hypersensitiveness to insulin was noted[15,16] not infrequently in the early years of its use, before the foreign proteins had been adequately removed. These reactions usually took the form of serum sickness, although an occasional case of true anaphylaxis has been reported.

Rarely hypersensitiveness to highly purified insulin occurs. Tufts[17] reported the case of a woman, aged sixty-two years, who had been given insulin six months previous during the treatment of diabetic gangrene by amputation. After treatment for several weeks with insulin during an attack of pyelonephritis, she suddenly became nauseated following an injection, with urticaria, and after a later injection the same symptoms returned, with marked edema of the arms and left leg. Insulin was discontinued and there was no recurrence of the reaction.

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CHAPTER XVII.

DIABETES ASSOCIATED WITH THYROID AND OTHER ENDOCRINE DISTURBANCES.

Since the presence of hyperglycemia and glycosuria in cases of hyperthyroidism is not rare, there is naturally a tendency to connect the disease with diabetes. John[1] points out that there is no definite relationship between the severity of hyperthyroidism or the height of the basal metabolism and the degree of hyperglycemia. It is natural to assume, therefore, that this is not due to the action of the thyroid itself, but is due to a deficiency in insulin formation, which is brought to light by the strain of hyperthyroidism.

The basic effect of thyroid secretion on carbohydrate metabolism is in promoting the discharge of glycogen from the liver. In the handling of a case of this type it is important to remember that the liver must be restocked with glycogen before any serious operative procedures are attempted. The relationship between the two glands is not direct but through the intermediary of their effects on carbohydrate storage. Consequently we would expect no constant pathological appearances in the pancreas to be associated with diabetes in the presence of hyperthyroidism.

Holst[2] found in 10 autopsied cases of diabetes associated with hyperthyroidism that there was no change in the pancreas in 4; in 6 cases, however, the pancreas was small and in 4 of these the number of the islands of Langerhans was diminished. It is important in this connection to keep in mind the great difficulties facing any estimate of the numbers of islands present in the human pancreas and the wide range in number of islands known to be present normally.[3]

Various degenerative changes in the islands, particularly necrosis or round-cell infiltration, have been reported. It is possible to see how hydropic degeneration of the insular epithelium might be present through long-continued functional strain and possibly fibrosis may eventually develop in the islands.

However, other changes are very difficult to associate. I have had an opportunity to study the pancreas of several cases of severe

and long-continued hyperthyroidism when the tissue was obtained very fresh. In the pancreas of these cases there was no change demonstrable. Garrod,[4] however, mentioned the occurrence of atrophic lesions of the pancreas in certain cases of exophthalmic goiter.

Joslin and Lahey[5] give the causes of death in 20 cases of diabetes complicated by hyperthyroidism.

TABLE 39.—CAUSES OF DEATH IN FATAL CASES OF DIABETES COMPLICATED BY HYPERTHYROIDISM.

Case No.	Cause of death.
A. Primary hyperthyroidism:	
377	Coma.
1836	Coma.
3734	Coma and pneumonia.
5176	Coma, thyroid storm, pulmonary infarcts.
4157	Cardiac.
3072	Arteriosclerosis, cerebral.
3234	Pneumonia.
4289	Septicemia.
5335	Cancer of pancreas.
4103	Inanition.
3911	Postoperative shock.
1901	?
B. Secondary hyperthyroidism:	
2473	Coma.
3500	Coma.
3860	Cardiac.
3956	Pneumonia and uremia.
3659	Postoperative hyperthyroidism.
4816	Postoperative hyperthyroidism.
C. Type unknown:	
869	Coma.
2272	Coma following cervical abscess.

A good deal of evidence has been produced for the occurrence of hypertrophy of the islands in cases of hypothyroidism or after thyroidectomy. One of the most interesting clinical evidences of this relationship is the one cited by Rohdenburg,[6] in which a woman, aged thirty years, was found to be glycosuric and in spite of treatment could not be made sugar-free. When forty years of age the menopause began, and after this she became sugar-free. She died of nephritis three years later, and at autopsy the thyroid showed a marked strumitis with almost complete destruction of the alveoli. The head of the pancreas was markedly fibrosed; in the body of the pancreas many of the islands were hypertrophied, some reaching three or four times the normal size.

Another instructive case is cited by Wilder.[7] This was a boy

who developed diabetes when fifteen months of age. For six months he was kept on a fairly rigid diet, and then this was somewhat relaxed without any evidence of glycosuria. A diagnosis of hypothyroidism was made when he was three years of age and with the institution of thyroid feeding intense glycosuria and acidosis developed. The thyroid administration was then discontinued and the tolerance increased, so that the child could eat anything without excreting sugar. When seen by Wilder he was seven years of age and showed typical juvenile myxedema. The basal metabolic rate was −45 and the blood sugar 0.12 per cent. Through administration of thyroid the metabolic rate was gradually raised to −10 and at that point sugar appeared in the urine. As much as 20 grams per day were excreted with a blood-sugar level of 0.145 per cent. Although the child gained in weight and strength, sugar was present in the urine on a diet with a glucose equivalent of 76 grams and 10 units of insulin daily.

In the present series I have been able to study 5 autopsied cases of diabetes associated with hyperthyroidism. As can be seen from Table 40, the ages range from twenty-nine to sixty-seven years. The cases occur preponderantly in the female.

Table 40.—Diabetes Associated with Hyperthyroidism.

No.	Age, yrs.	Sex.	Duration of diabetes, yrs.	Pancreas.			Cause of death.
				Size.	Islands.	Acini.	
4289	30	♀	0.2+	30 gm.	Negative	Negative	Coma
A27-82	38	♂	6.0	⅓ normal	Few, fibrosed	Marked fibrosis	Hyperthyroidism
DA26-25	43	♀	2.7	Normal	Negative	Slight fibrosis	Coma
5335	67	♀	3.3	Large	Negative	Carcinoma	Carcinoma of pancreas
DA27-32	39	♀	6.5	70 gm.	Negative	Negative	Rheumatic carditis

There is absolutely no characteristic picture in the pancreas. In fact, the islands were negative in all except 1 case, where their number was apparently somewhat decreased and they showed varying degrees of fibrosis. The cause of death of one of the cases was carcinoma of the pancreas, but many of the islands persisted uninjured in the midst of the carcinomatous tissue.

DIABETES AND HYPOPHYSIS.

There have been numerous efforts to link together diabetes and pathological changes in the pituitary gland. The studies of Cushing have shown that there may be a definite association between pituitary hypersecretion and glycosuria, which at times takes on the characteristics of true diabetes.

In my series I encountered only 1 case, A16-06, from the Peter Bent Brigham Hospital. This was a woman, aged fifty-one years, with marked acromegaly. Diabetes had been present for one year. The pancreas was essentially negative, although there was a possibility of slight hydropic degeneration in some of the epithelial cells of the islands. There was a moderate amount of glycogen in the liver cells and a slight amount in the nuclei of the liver cells. The epithelium of Henle's loops also showed a moderate amount of glycogenic infiltration. The cause of death was diabetic coma.

DIABETES ASSOCIATED WITH OTHER ENDOCRINE DISTURBANCES.

Inasmuch as I have encountered no instances of diabetes associated with endocrine disturbances other than those referable to the thyroid and pituitary glands, I shall defer the discussion of such cases to the next chapter, where the various possible etiological factors in diabetes will be considered.

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CHAPTER XVIII.

THEORIES AS TO THE ETIOLOGY OF DIABETES.

However diverse the underlying etiological factors may be, diabetes mellitus has one immediate cause: insulin deficiency. This deficiency may be actual, through lessened production, through neutralization of insulin by hypothetical substances, by failure of insulin transport from the islands; or it may be relative, through increased demand or through insufficient facilities for the formation and storage of glycogen.

At one end of the scale we have the relatively easily understood cases of diabetes developing after extensive destruction of pancreatic tissue, either suddenly (and rarely), as in acute pancreatitis, or gradually, as in hemochromatosis. At the other end we have the cases, so difficult of explanation, in which the various organs are apparently normal although the diabetes is severe. However, even here insulin deficiency is demonstrated by the abnormal glycogen distribution and by the therapeutic effect of insulin.

The evidence is overwhelming that whatever the distribution of insulin in the tissues, whatever the possible sources of supply, the islands of the pancreas are of outstanding importance for insulin production. Table 41 from Joslin[1] illustrates the insulin content of various human tissues.

Table 41.—Insulin Content of Human Tissues.*

Case No.	Cause of death.	Units of insulin per 100 grams tissue.					
		Pancreas.	Liver.	Kidneys.	Heart.	Thyroid.	Spleen.
Diabetic:							
127 . .	Gangrene, coronary thrombosis	14.7	1.2	1.6	1.1	..	1.0
3592 . .	Multiple abscesses	2.5	0.9	1.9	2.2	..	2.2
4289 . .	Septicemia	25.0	3.0	10.0	3.0	9.0	..
Non-diabetic .	Cancer of pancreas	70.0	..	..	..	..	..
	Pulmonary embolism	87.0	25.0	116.6	..	..	90.0
Baker, Dickens and Dodds[2]	Myocardial degeneration	108.0	..	11.5	..	..	..
	Diabetic coma	42.5	16.3	..	..	..	..

* See also Brugsch, H.: Ztschr. f. d. ges. exper. Med., 1929, **65**, 574.

While no case of "complete" permanent diabetes has been encountered by Joslin or by von Noorden, a pancreas in which no insular tissue is present does not occur or at least is extremely rare.

Anatomical causes of insulin deficiency are well known, and may act either by destruction or deficiency of insular epithelium, by this destruction combined with a barrier interposed between blood vessels and epithelium, as in the case of hyalinization and fibrosis, or deficient blood supply.

ANATOMICAL CAUSES OF INSULIN DEFICIENCY.

I. Destruction of pancreatic tissue (both insular and acinar).
   1. Pancreatitis.
      (*a*) Acute.
      (*b*) Chronic.
   2. Malignant disease.
      (*a*) Primary.
      (*b*) Metastatic.
   3. Hemochromatosis.
   4. Toxic injury.

II. Selective destruction of insular tissue.
   1. Hyaline infiltration.
      (*a*) Amyloid infiltration.
   2. Fibrosis.
   3. Toxic injury and lymphocytic infiltration.
   4. Hydropic degeneration.

III. Inadequate insular tissue (congenital deficiency).

IV. Inadequate blood supply.
   1. Arteriosclerosis.

These various causes of insulin deficiency have been considered in detail in Chapter III, and so are merely catalogued here. Insulin insufficiency in such cases is easily understood, although frequently a considerable amount of insular tissue apparently capable of functioning is present.

The mechanism by which selective destruction of the islands takes place is obscure, except in the case of toxic injury, where the abundant blood supply and intimate contact of the epithelium with the blood stream affords unusual exposure to circulating toxins, and in the case of hydropic degeneration, definitely related with functional overstrain.

What part functional overstrain may play in the production of

other lesions in the islands, or in diabetes without anatomical changes, is open to question.

The occurrence of hyalinization of the islands in the older age groups, when thickening of the walls of the arterioles is very common, particularly in the spleen, suggests that this hyaline may be associated with early changes in the insular vessels or, perhaps, even with physiological involutions secondary to age.

In any case, the pathology of the pancreas in diabetes cannot be considered as static. As seen at any one time it represents a balance struck between the factors tending to produce degenerative changes of the islands and the regenerative powers of the pancreas. That these latter are by no means inconsiderable has been shown by the experimental work of Bensley[3] and his pupils, the observations of Boyd,[4] and is evidenced also by the not infrequent occurrence of mitotic figures in islands, a portion of whose epithelium has been injured. (See also page 155.) The important rôle played by hemochromatosis in elucidating the process I have already stressed. "We find . . . variation in involvement of the islands [in hemochromatosis] . . . ranging from the remains of islands represented by clusters of pigment-loaded endothelial leukocytes and fibroblasts in the stroma to islands without pigment and apparently normal. The conclusion is inevitable that new islands are being formed to take the place of those destroyed by the pigment deposits. In further substantiation of this evidence, occasional mitotic figures can be found in the cells of the younger, pigment-free islands.

"The pigment is not restricted to the island cells, but affects the acinar tissue as well. The same evidence of regeneration is offered by the acinar cells as by those of the islands.

"The well-established evidence of destruction and regeneration of parenchymal cells in the liver offers a striking parallel to the changes in the pancreas in hemochromatosis. Just as in the liver the parenchymal cells show every stage from newly-formed pigment-free cells through those containing hemofuscin and those containing hemosiderin to necrotic cells, the same steps can be traced in the acinar and island cells of the pancreas."[5]

The pancreas in diabetes is not simply the scarred field of an old battle ground, but is the actual field of conflict. It does not submit without a struggle to injury, but endeavors to regenerate. The reason that we have no total diabetes is because we have no cases in which destruction of the insulin-producing tissue has been com-

plete. Even in cases where injury is most severe there is not total destruction of insular tissue, but some is still present and endeavoring to carry on. This conception explains the gradual development of the disease through slow but progressive destruction of the islands and the failure of regeneration to make good the loss. It explains the improvement of tolerance, fortunately now occasionally encountered, as the regenerative power of the pancreas outstrips the destruction of the pancreatic tissue by the injurious agent.

This leads to the hope that in young people, with their more resilient tissues, proper treatment may remove the cause of injury and favor more or less complete restoration of the damaged islands.

HYPOPHYSEAL DIABETES.

In the effort to find some explanation for the occurrence of diabetes in the absence of pancreatic pathology, clinical observation has led to the suggestion that pituitary disease is responsible for a certain number of cases. Marie,[6] in describing acromegaly as a clinical entity, noted that diabetes occurred in 2 of his first 4 cases, and with the accumulation of case reports a definite relationship between these diseases became evident. The association of pituitary tumors and glycosuria had already been noted by Loeb.[7]

Naunyn,[8] following Loeb,[9] who preferred a neurogenic to an endocrine explanation for these cases, assumed the hypophyseal tumors caused pressure, direct or transmitted, on a "sugar center." This explanation was combated by Lorand,[10] who pointed out the occurrence of both brain tumor and acromegaly without diabetes. Cushing,[11] in an admirable series of clinical observations and experiments, has produced strong evidence of the association of glycosuria with excess secretion of the posterior lobe, and conversely the association of an abnormally high carbohydrate tolerance with hyposecretion. An excellent survey of the published articles on this subject was made by Colwell[12] in 1927.

Presumptive evidence of the relationship of diabetes and changes in the pituitary gland are the studies by White[13] and Joslin,[14] emphasizing the occurrence of diabetes among children who are taller than the ordinary.

Table 42 gives some idea of the great frequency of diabetes, or better glycosuria, in acromegaly.

TABLE 42.—FREQUENCY OF GLYCOSURIA IN ACROMEGALY.

Author.	Cases of acromegaly.	Number showing glycosuria.	Per cent.
Hansemann[15]	97	12	12
Hinsdale[16]	130	14	11
Williamson[17]	21	6	29
Borchardt[18]	176	71	40
Anders[19]	88	16	18
Rosenberger[20]	196	82	42
Cushing and Davidoff[21]	100	25	25
Total	808	226	28

The association of diabetes and hypersecretion of the pituitary may be considered from various angles: 1. Mere coincidental occurrence of the two diseases, while conceivable, is capable of explaining only a few cases, and may be herewith dismissed.

2. Definite lesions in the hypophysis may be associated with diabetes and may directly influence carbohydrate metabolism.

3. Changes in pituitary secretion may affect: (*a*) the insulinogenic ability of the pancreas, (*b*) the action of insulin and (*c*) the storage of glycogen.

4. Changes in the pituitary itself may produce pressure on adjacent nerve centers which affect carbohydrate metabolism.

Attempts have been made to explain the ordinary type of diabetes on the basis of pituitary lesions. Fry[22] has described adenomatous proliferation of eosinophilic cells in the anterior lobe, areas of cellular degeneration and "colloid invasion" as characteristic of diabetes mellitus. Kraus[23] found similar lesions in the pituitary glands of 10 diabetics between fourteen and forty-one years of age, and in 2 of 12 cases over forty-one years of age.

I have had an opportunity to study the hypophysis in 27 cases of diabetes free from stigmata of pituitary disease, but in all of these cases the interval after death was short and good histological detail obtained. In no case did I find significant variations from the normal.

Cases of so-called "hypophyseal diabetes" have been described, characterized by marked polyuria, mild glycosuria showing but little change in spite of marked variations in the diet, and occasionally spontaneous cure. However, only 1 of the 4 cases reported by Brugsch[24] gave good evidence of pituitary damage. Steensma[25] has also reported a case.

The indirect evidence is of some value. Cases of hypopituitarism have long been known to show increased carbohydrate tolerance.[26]

However, there are far too many difficulties in the way of assuming that the pituitary gland itself is a constant or even important factor in the control of carbohydrate metabolism. Certainly no one lesion is involved.

One important difference between ordinary diabetes mellitus and that associated with hyperpituitarism is the tendency of the latter type to remain mild and even to regress. Two cases of Cushing (cited by Colwell[12]) are known to have regressed after relief of pressure from the pituitary tumor.

The possibility that changes in the pituitary may hinder insulin formation by the pancreas is slight. Colwell[12] has collected 15 cases of acromegaly showing pancreatic changes, which may be classified as follows: fibrosis, atrophy, hypertrophy, pancreatitis (hemorrhagic and suppurative), hyalinized islands, diminution of number of islands and hyperplasia of island cells. Certainly no distinctive effect on the pancreas can be detected here.

Interference with the action of insulin by hypersecretion of the pituitary is unlikely because diabetes is far from constant in acromegaly, and because insulin administered to these cases is as effective as insulin administered to cases of typical diabetes.

Mechanical stimulation of the hypophysis produces a transient glycosuria as does injection of extract of the posterior lobe.[27] This is presumably due to a discharge and hydrolysis of stored glycogen, although whether the effect is direct, by way of the adrenal glands, or by way of the nervous system is open to question.

The experiments of Sachs and MacDonald[28] indicate that the effect may be due to stimulation of the hypothalamus rather than to direct action of the pituitary gland.

The administration of ergotamine, which prevents glycogenolysis, inhibits the antagonistic effect of pituitary extract and insulin.

Diabetes may occur in cases where the hypophysis and nearby structures are involved, even in the absence of acromegaly. Colwell[12] collected 38 such cases from the literature.

The work of Beattie[29] and his collaborators emphasizes the importance of the hypothalamic region in the control of sugar metabolism through the action of the posterior hypothalamic nuclei on adrenalin secretion.

Thus we may conclude that pituitary diabetes may best be considered as neurogenic diabetes, except for those cases in which excessive secretion produces glycogenolysis.

ADRENAL DIABETES.

While adrenalin has long been known to produce hyperglycemia and glycosuria, it cannot be considered as a direct factor in the production of diabetes. Hypoglycemia, on the other hand, has occurred in Addison's disease.[30] The antagonism between insulin and adrenalin is well known. In my series of 300 autopsies no significant lesions were encountered in the adrenals.*

NEUROGENIC DIABETES.

The occurrence of emotional glycosuria, the loss of tolerance due to mental strain in the course of diabetes, the sugar puncture of Claude Bernard, all point to a close relationship between the central nervous system and the pancreas. Intermediate action of the adrenals in the case of emotional glycosuria is quite possible. The World War, in spite of tremendous emotional strain on millions of persons, did not provide any noticeable increase in the number of diabetic cases.

The probable importance of lesions in the hypothalamus cannot yet be fully evaluated, owing to lack of data. As stated above, very probably hypophyseal diabetes is in reality neurogenic.

RELATION TO GONADS.

The two peaks of incidence of diabetes occur at the time of puberty in children[31] and the time of menopause in adults.[32] Disturbances of interrelationships between the various endocrine glands and marked variations in metabolism undoubtedly occur at these times and might well precipitate a latent diabetes.

HEREDITY.

The difficulty of separating hereditary and environmental factors is so great that data are as yet insufficient for determining the exact rôle of heredity.

In children the incidence of heredity is constantly rising the

*Colwell, A. R. and Bright, E. M.; (Am. Jour. Physiol., 1930, **92**, 555) found adrenalin to stop oxidation of glucose when injected intravenously at a rate of 0.001 mg. per kg. per minute, while a constant intravenous supply of glucose is maintained. Although they were unable to reproduce the effects of pancreas extirpation, nevertheless excessive secretion of adrenalin may be an important means by which sympathetic nervous system disease may produce functional changes in the pancreas.

longer the child is under observation, which allows obviously a greater opportunity for the disease to develop and to be detected in the relatives. In Joslin's diabetic children who lived about two years, the heredity was 20 per cent. However, when living children are considered, 40 per cent of those who have had the disease five years have positive heredity, and among those whose diabetes antedates the discovery of insulin, the incidence is 45 per cent.

OBESITY.

The importance of obesity, usually an evidence of chronic overeating, as a predisposing factor in the production of diabetes has been well emphasized by Joslin[33] and others. Obesity may be regarded as indubitable evidence of abnormal food intake, and hence of abnormal strain on the islands of Langerhans.

GLYCEMIN.

Loewi's[34] glycemin, a hormone-like substance supposedly formed in the liver which prevents the utilization of glucose by the cell, might explain those puzzling cases of diabetes which yield no anatomical evidence of pathology. However, the existence of this substance has not been confirmed.[35]

EPSTEIN'S HYPOTHESIS.

One of the most interesting hypotheses is that put forward by Epstein,[36] who makes use of the known antagonism between insulin and trypsin. Through changes in endothelial permeability, trypsin finds its way into the capillaries. The trypsin neutralizes the insulin secreted into the blood stream, inactivating it, and also when the trypsin is carried to the liver it provokes glycogenolysis, resulting in hyperglycemia and glycosuria.

Another theory based on alterations of permeability of vascular endothelium is that of Wiechmann,[37] who considers that the endothelium remains permeable to glucose entering the blood stream, but is not permeable to glucose leaving the vessels.

INFECTION.

While the temporary unfavorable effect of infectious diseases in diabetes is established beyond all equivocation, and infection is now the cause of most hospital admissions of diabetic patients, as a

direct cause of the disease it is of little importance. Histological resemblances between pancreas and parotid have led to special interest in mumps,[38,39] but this disease can be but rarely blamed for diabetes.

Severe toxic injury to the islands in the course of various infections may produce either transient glycosuria or more rarely true diabetes. Root and I[5] have called attention to the actual necrosis of insular epithelium that may occur in such cases, and also to evidences of regeneration. Of course, if diabetes is already present such injury lowers tolerance.

The suggestion of Bergey,[40] that diabetes is itself a transmissible infectious disease, has not been confirmed. The same holds true for the plasmodium of Rasch.[41]

CASES WITH NO SIGNIFICANT PATHOLOGY.

There remains to be explained the intriguing group of cases without definite anatomical change in the pancreas or other organs. Even the granules in the island cells may appear normal. In my series of 300 diabetic autopsies the pancreas was available for detailed histological study in 259. Of these, 69 were normal so far as could be determined. No lesions in other organs were sufficient to explain the existence of diabetes, although the pituitary was examined in only a small proportion. However, no evidence of clinical disturbance other than the diabetic process was encountered.

These cases in which changes in the pancreas are absent or too trifling to merit consideration have always puzzled and irritated the pathologist. It is difficult to conceive of long-continued and profound functional pathology without organic change, the field of mental disease excepted.

Since the amount of insulin demanded fluctuates between wide limits, some rapidly functioning regulatory mechanism must exist for the output of insulin. Obviously the amount utilized in absorbing a heavy meal would produce marked hypoglycemia if secreted in a fasting period; the intravenous glucose solution so frequently used by surgeons puts a heavy and sudden demand on the insulin-producing mechanism, yet this is readily met. In the absence of prompt control, we would swing ceaselessly and dizzily from hyperglycemia to hypoglycemia and back.

This regulation may be accomplished by alterations in rate of secretion, which is partially dependent on the amount of blood pass-

ing through the islands, or by alterations in amount of blood-flow, which determines not only the nutrition of the island cells but the amount of insulin transported from the islands.

In examining the living pancreas of the mouse by a modification of Covell's[42] method, using transmitted light, I found in the thinner portions of the pancreas reddish-white spots which faded slightly from time to time and others appeared. Subsequent histological examination indicated these spots to be islands of Langerhans. Thus, we may have an intermittent circulation of blood through the islands, and a very simple and rapid means of regulating the output of insulin. Such an intermittent circulation might well be expected in view of the known intermittent circulation in the glomeruli, the peripheral capillaries and elsewhere.*

Emotional glycosuria might well be explained on the basis of transient circulatory changes, and the action of adrenalin might be exerted in part on the vessel walls and in part through glycogenolysis.

If we assume the existence of a spasm affecting the insular blood vessels, similar let us say to that of the peripheral arterioles in Raynaud's disease, we at once have an explanation of the anomaly of normal islands with deficient insulin production.

Insulin in the epithelium of the islands is worth no more than coal in the mine. It must be transported to the point of consumption to be of value. Until transported, it might as well be non-existent.

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APPENDIX A.

METHODS.

Through careful studies made postmortem on the bodies of diabetic patients the clinical information obtained during the course of their disease can be correlated with the anatomical findings and the knowledge thus gained made available for other sufferers. As Joslin says, "An operation during life is attended by pain and is for the benefit of the individual; an operation after death is free from pain and is for the benefit of humanity."

Clinical observation and evidence at autopsy suggested the correlation of diabetes mellitus with diseased islands of Langerhans. Clinical observation, examination of surgically removed pancreatic tissue, and autopsy proved that the islands produced insulin. The same methods may some day enable us to unravel the as yet but dimly understood etiology of the disease.

To quote from the motto on the wall of the postmortem room, "Mortui vivos docent"—the dead teach the living. The responsibility for the success of the autopsy rests directly upon the pathologist. His is the duty of seeing that all possible information is gleaned. His is the duty of seeing that the autopsy is performed in a seemly manner and that the needs of the undertaker are sympathetically considered. If he neglects the first, it is futile for the internist to obtain permission for the autopsy. If he neglects the second, it is impossible for the internist to obtain permission.

The autopsy room at the Palmer Memorial Hospital, which also serves the Deaconess, is next to the pathologist's office. Thus, he is sure it is neat and clean at all times. An operation performed after the patient's death deserves as dignified surroundings as one before death. The presence of a nurse is desirable.

There are certain features which must be especially considered in autopsies on diabetic patients. The weight of the patient is important, and this is easily obtained. A small chain hoist is hung from the ceiling and a spring scale (Chatillon) suspended from this,

with a spreader and four hooks below. The truck on which the body lies is grasped by the hooks and the whole raised by the chain hoist. A tare hand, previously set for the weight of spreader, hooks and truck, permits direct reading of the net weight.

Since the pancreas is extremely labile and since glycogen in tissues rapidly hydrolyzes, it is essential that autopsy be performed as soon after death as practicable. If any long period of delay is anticipated, the body should be placed in the cold chamber promptly.

FIG. 84.—Postmortem room for the Deaconess and Palmer Memorial Hospitals illustrating grid-top-type table with air suction through the base.

The following autopsy technique is used in this laboratory. A useful primary incision is the Y type, from over each acromial prominence to the sternum at the level of the third ribs, and thence in the mid-line to the pubis, passing just to the left of the umbilicus. This affords an excellent exposure, and yet burial may be carried out in low-necked clothing without any trace of the incision visible.

In an autopsy on a diabetic the pancreas should be removed first. A good exposure is obtained by cutting through the gastro-colic omentum. The pancreas is freed at the tail and stripped upward and to the right, avoiding all unnecessary trauma or compression. The portion of the head most closely adherent to the duodenum is cut away and left in place, after any abnormalities of the gland

have been noted and interpreted. The greater portion of the pancreas is removed and weighed. Transverse sections, 1 to 2 mm. in thickness, are cut and placed in the various fixing fluids. While this is being done, an assistant should take thin sections of skin, striated muscle and liver and place them in absolute alcohol for subsequent staining for glycogen.

The autopsy may then proceed in the normal manner. As soon as the heart is exposed, a sample of blood is taken for blood sugar and non-protein nitrogen determination. The heart is examined for any evidences of myocardial or valvular lesions, the coronaries opened as far down their finer branches as possible. Sections are taken from various portions and placed in separate bottles. Electrocardiograms have been taken on the majority of the patients and correlation between the pathological and electrocardiographic findings is being attempted. Sections are also placed in absolute alcohol for glycogen stains.

The only other variation from the usual routine is careful dissection of the remaining pancreatic tissue from the duodenum. This is weighed, its weight added to the other portion and sections taken.

Particular attention is paid to the vascular system. Portions of the aorta are taken for chemical analysis.

A great assistance to the undertaker is the ligation separately of the innominate, left common carotid and left subclavian arteries. The ends of the ligatures are left outside when the primary incision is sewed up.

If permission has been given to open the head, the carotid arteries should also be ligated just within the cranial cavity.

Routine fixation is most satisfactorily accomplished in Zenker's fluid and in 10 per cent neutralized formalin. Absolute alcohol is used for all tissues in which the glycogen content is to be studied. Regaud's fixation is most satisfactory for the hypophysis.

The following additional fixing fluids are used for the pancreas:

1. Zenker's fluid without acetic acid.
2. Helly's fluid.
3. Regaud's fluid.
4. Champy's fluid.

Potassium dichromate	3 per cent	21 cc.
Chromic acid	1 "	21 "
Osmic acid	2 "	12 "

5. Zenker-osmic acid.

Zenker's fluid without acetic acid . . .		25 cc.
Osmic acid	2 per cent	5 "

6. Osmic chromic fluid.

Osmic acid	2 per cent	4 cc
Chromic acid	1 "	30 "
Acetic acid	glacial	1 "

All pancreatic tissue fixed in fluids containing osmic acid should be freed from fat so far as possible.

Oil of cedar rather than chloroform is best for clearing the pancreas.

Of course the smaller the blocks of tissue the easier it is to get thin sections, and on properly fixed material sections 2.5 micra thick can be fairly readily obtained. A large number of different stains may be utilized. We have found the following list satisfactory.

For general examination:

1. Phloxine-methylene blue or eosin-methylene blue.
2. Goodpasture's eosin-methylene blue.
3. Masson's iron hematoxylin-Van Gieson.

For demonstration of fibrosis and hyaline:

1. Mallory's aniline blue.
2. Mallory's phosphotungstic acid hematoxylin.
3. Masson's iron hematoxylin-fuchsin-lumiere green.

For demonstration of specific granules:

1. Bensley's modification of Mallory's aniline blue. (See page 26.)
2. Bensley's neutral gentian.
3. Ukai's stain.

For demonstration of mitochondria:

1. Regaud's iron hematoxylin.
2. Altmann's aniline fuchsin-methyl green.

For demonstration of glycogen:

1. Best's carmine stain.

The diagnosis of hemochromatosis in a living patient is sometimes uncertain, and its importance is so great from the standpoint of prognosis and from the probability of insulin resistance that biopsy is justifiable. A small portion of skin, including the subcutaneous tissue, should be excised from any suspiciously pigmented area. This should be fixed in alcohol-formalin, imbedded in celloidin, sectioned, stained for iron with potassium ferrocyanide by Mallory's method, and counterstained with basic fuchsin. Granules of hemofuscin or hemosiderin present in the skin may be readily demonstrated by this method.

APPENDIX B.

THE CAUSES OF DEATH IN DIABETES.

NUMBER OF DEATHS FROM IMPORTANT CAUSES AND PER CENT THESE ARE OF ALL CAUSES AMONG 1294 DECEASED DIABETICS AUGUST 7, 1922 TO DATE. EXPERIENCE OF ELLIOTT P. JOSLIN, M.D., BOSTON, MASS.

Cause of Death.	Banting Era total.	
	Deaths.	Per cent of all causes.
All causes	**1294**	100.0
1. (*a*) Primary coma	**199**	15.4
(*b*) Coma incidental to other causes	48	3.7
2. Cardio-renal-vascular diseases—total	**597**	46.1
Cardiac	273	21.1
Nephritis	57	4.4
Apoplexy	99	7.7
Arteriosclerosis—total	60	4.6
Arteriosclerosis with cardiac, renal or cerebral complications	38	2.9
Gangrene	108	8.3
3. Infections—total	**212**	16.4
Influenza and pneumonia	105	8.1
Other respiratory infections	7	0.5
Infections of the pharynx and tonsils	3	0.2
Infections of the ear and mastoid	7	0.5
Gall bladder disease	5	0.4
Appendicitis	11	0.9
Other infections of the digestive system	5	0.4
Carbuncle	18	1.4
Erysipelas	8	0.6
Abscess of the skin	14	1.1
Abscess of other organs	16	1.2
All other infections	13	1.0
4. Pulmonary tuberculosis	**74**	5.7
5. Cancer	**92**	7.1
6. Syphilis	**1**	0.1
7. Other causes	**119**	9.2
Inanition	6	0.5
Acute intestinal obstruction	2	0.2
Cirrhosis of the liver	10	0.8
Diseases of the prostate	10	0.8
Diseases of the thyroid gland	6	0.5
Pregnancy	5	0.4
Accidents	26	2.0
Suicides	9	0.7
Diabetes	13	1.0
Other diseases and conditions	32	2.5

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